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(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

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(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): HENNEQUIN, Laurent, François, André [FR/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agents: BRYANT, Tracey et al.; Astrazeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

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(57) Abstract: The invention relates to compounds of the formula (I): wherein: ring C is 9 or 10-membered bicyclic heteroaromatic group containing at least one nitrogen atom in the ring attached to Z and optionally containing a further 1-3 heteroatoms, selected independently from O, S, and N, with the proviso that ring C is not a quinazoline, quinoline or cinnoline group; either any one of G₁, G₂, G₃, G₄ and G₅ is nitrogen and the other four are -CH-, or G₁, G₂, G₃, G₄ and G₅ are all -CH-; Z is -O-, NH-, -S-, CH₂- or a direct substituents R¹ may be attached at any free carbon atom of the indole, azaindole or indazole group; m is an integer from 0 to 2; R^b represents hydrogen or another value as defined herein; R¹ represents hydrogen, hydroxy, halogeno, C₁-alkyl, or any other value as defined herein; R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁-alkyl, C₁-alkoxy, C₁-alkylsulphonyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁-alkyl), or R⁵X¹ (wherein R⁵ and X¹ are as defined herein) and salts thereof, processes for the preparation of such compounds, pharmaceutical compositions containing a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient and the use of a compound of formula (I) in the manufacture of a medicament for the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals. The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.

-1-

CHEMICAL COMPOUNDS

The present invention relates to indole, azaindole and indazole derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

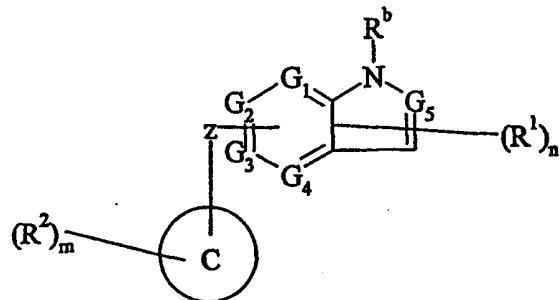
Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

- characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other
- 5 intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another
- 10 fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.
- 15 The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar
- 20 formation and adhesions, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against epidermal growth factor (EGF) receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be
- 25 used in an amount sufficient to inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against EGF receptor tyrosine kinase. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against FGF R1 receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to
- 30 inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against FGF R1 receptor tyrosine kinase.

-3-

According to one aspect of the present invention there is provided the use of a compound of the formula I:

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(I)

wherein:

- ring C is a 9 or 10-membered bicyclic heteroaromatic group containing at least one nitrogen atom in the ring attached to Z and optionally containing a further 1-3 heteroatoms, selected independently from O, S and N, with the proviso that ring C is not a quinazoline, quinoline or cinnoline group;
- either any one of G₁, G₂, G₃, G₄ and G₅ is nitrogen and the other four are -CH-, or G₁, G₂, G₃, G₄ and G₅ are all -CH-;
- Z is -O-, -NH-, -S-, -CH₂- or a direct bond; Z is linked to any one of G₁, G₂, G₃ and G₄ which is a free carbon atom;
- n is an integer from 0 to 5; any of the substituents R¹ may be attached at any free carbon atom of the indole, azaindole or indazole group, such free carbon atoms may be G₁, G₂, G₃, G₄ or G₅ or may be at the 3-position of the indole, azaindole or indazole group;
- m is an integer from 0 to 2;
- R^b represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₃alkylaminoC₁₋₄alkyl, di(C₁₋₃alkyl)aminoC₁₋₄alkyl, C₂₋₅alkenylaminoC₁₋₄alkyl, C₂₋₅alkynylaminoC₁₋₄alkyl, -C₁₋₅alkyl(ring A) wherein ring A is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino and wherein ring A may bear one or more substituents selected from C₁₋₄alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, hydroxy, oxo, halogeno, cyano, cyanoC₁₋₄alkyl, C₁₋₄alkylsulphonyl and C₁₋₄alkanoyl;

- R¹ represents hydrogen, oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₃alkylaminoC₁₋₄alkyl, di(C₁₋₃alkyl)aminoC₁₋₄alkyl, -C₁₋₅alkyl(ring B) wherein ring B is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-methylpiperazinyl, N-ethylpiperazinyl, morpholino and thiomorpholino;
- 5 R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphonyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO₂-, -NR⁶C(O)-, -C(O)NR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or
- 10 C₁₋₃alkoxyC₂₋₃alkyl), and R⁵ is selected from one of the following twenty-two groups:
- 1) hydrogen, oxiranylC₁₋₄alkyl or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
 - 2) C₁₋₅alkylX²C(O)R¹¹ (wherein X² represents -O- or -NR¹²- (in which R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different each represents hydrogen, C₁₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
 - 3) C₁₋₅alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO₂-, -OC(O)-, -NR¹⁷C(O)-, -C(O)NR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents
- 15 20 hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more
- 25 30 substituents selected from C₁₋₄alkyl));
- 4) C₁₋₅alkylX⁴C₁₋₅alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO₂-, -NR²³C(O)-, -C(O)NR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein

- R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R²⁸ (wherein R²⁸ is a 4-, 5- or 6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which
- 5 heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O)_f(C₁₋₄alkyl)_gringD
- 10 (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 6) C₁₋₅alkylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 7) C₂₋₅alkenylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 15 8) C₂₋₅alkynylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 9) R²⁹ (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁰R³¹, -NR³²C(O)R³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group -(O)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which
- 20 cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 25 10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 11) C₂₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 12) C₂₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-,-
- 30 SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

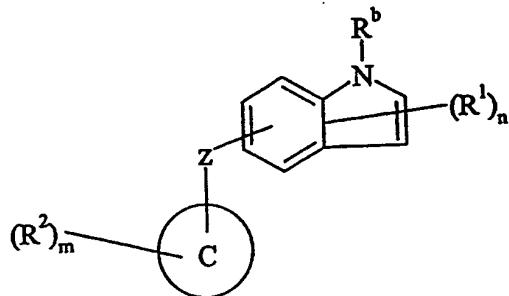
- 14) $C_{2-5}\text{alkenyl}X^7R^{29}$ (wherein X^7 represents -O-, -S-, -SO-, - SO_2 -, -NR³⁹C(O)-, -C(O)NR⁴⁰-, - $\text{SO}_2\text{NR}^{41}$ -, -NR⁴² SO_2 - or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 15) $C_{2-5}\text{alkynyl}X^8R^{29}$ (wherein X^8 represents -O-, -S-, -SO-, - SO_2 -, -NR⁴⁴C(O)-, -C(O)NR⁴⁵-, - $\text{SO}_2\text{NR}^{46}$ -, -NR⁴⁷ SO_2 - or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 5 16) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{29}$ (wherein X^9 represents -O-, -S-, -SO-, - SO_2 -, -NR⁴⁹C(O)-, -C(O)NR⁵⁰-, - $\text{SO}_2\text{NR}^{51}$ -, -NR⁵² SO_2 - or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 10 17) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 18) $C_{2-5}\text{alkenyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 15 19) $C_{2-5}\text{alkynyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20 20) $C_{2-5}\text{alkenyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 21) $C_{2-5}\text{alkynyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 20 22) $C_{1-4}\text{alkyl}R^{54}(C_{1-4}\text{alkyl})_q(X^9)_rR^{55}$ (wherein X⁹ is as defined hereinbefore, q is 0 or 1, r is 0 or 1, and R⁵⁴ and R⁵⁵ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6- membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl), with the proviso that R⁵⁴ cannot be hydrogen);
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-7-

and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino); or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

According to another aspect of the present invention there is provided the use of a compound of the formula I¹:

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(I¹)

wherein:

ring C is a 9 or 10-membered bicyclic heteroaromatic group containing at least one nitrogen atom in the ring attached to Z and optionally containing a further 1-3 heteroatoms, selected independently from O, S and N, with the proviso that ring C is not a quinazoline, quinoline or cinnoline group;

Z is -O-, -NH-, -S-, -CH₂- or a direct bond; Z is linked to the benz ring of the indole group at any of the positions 4-, 5-, 6- or 7- of the indole group;

n is an integer from 0 to 5; any of the substitutents R¹ may be attached at any free carbon atom of the indole group, such free carbon atoms may be at positions 2-, 3-, 4-, 5-, 6-, or 7- of the indole group;

m is an integer from 0 to 2;

R^b represents hydrogen, C₁₋₄alkyl, C₁₋₃alkoxyC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₃alkylaminoC₁₋₄alkyl, di(C₁₋₃alkyl)aminoC₁₋₄alkyl, -C₁₋₅alkyl(ring A) wherein ring A is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-methylpiperazinyl, N-ethylpiperazinyl, morpholino and thiomorpholino;

- R^1 represents hydrogen, oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, amino C_{1-4} alkyl, C_{1-3} alkylamino C_{1-4} alkyl, di(C_{1-3} alkyl)amino C_{1-4} alkyl, - C_{1-5} alkyl(ring B) wherein ring B is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-methylpiperazinyl, N-ethylpiperazinyl, morpholino and thiomorpholino;
- 5 R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylsulphanyl, - NR^3R^4 (wherein R^3 and R^4 , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or R^5X^1 - (wherein X^1 represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁶C(O)-, -C(O)NR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R^6 , R^7 , R^8 , R^9 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or
- 10 C_{1-3} alkoxy C_{2-3} alkyl), and R^5 is selected from one of the following twenty-two groups:
- 1) hydrogen, oxiranyl C_{1-4} alkyl or C_{1-5} alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
 - 2) C_{1-5} alkyl $X^2C(O)R^{11}$ (wherein X^2 represents -O- or -NR¹²- (in which R^{12} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{11} represents C_{1-3} alkyl, - $NR^{13}R^{14}$ or -OR¹⁵ (wherein R^{13} , R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-5} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
 - 3) C_{1-5} alkyl X^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, -SO₂-, -OC(O)-, -NR¹⁷C(O)-, -C(O)NR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R^{17} , R^{18} , R^{19} , R^{20} and R^{21} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{16} represents
- 20 hydrogen, C_{1-3} alkyl, cyclopentyl, cyclohexyl or a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3} alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4} cyanoalkyl, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl, C_{1-4} alkoxycarbonyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkylamino C_{1-4} alkoxy, di(C_{1-4} alkyl)amino C_{1-4} alkoxy and a group -(O)_f(C_{1-4} alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more
- 25 substituents selected from C_{1-4} alkyl));
- 4) C_{1-5} alkyl X^4C_{1-5} alkyl X^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³C(O)-, -C(O)NR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein

-9-

- R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R²⁸ (wherein R²⁸ is a 4-, 5- or 6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which
- 5 heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0
- 10 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 6) C₁₋₅alkylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 7) C₂₋₅alkenylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 15 8) C₂₋₅alkynylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 9) R²⁹ (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁰R³¹, -NR³²C(O)R³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which
- 20 cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 25 10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 11) C₂₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 12) C₂₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -
- 30 SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

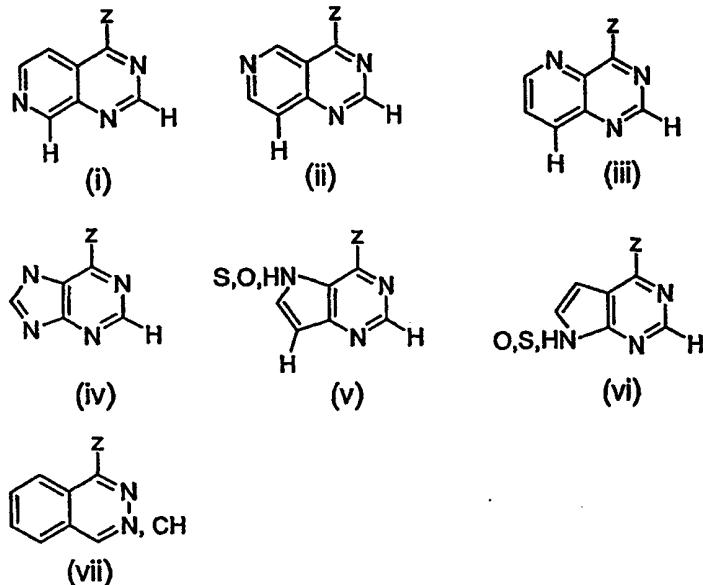
-10-

- 14) $C_{2-5}\text{alkenyl}X^7R^{29}$ (wherein X^7 represents -O-, -S-, -SO-, -SO₂-, -NR³⁹C(O)-, -C(O)NR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 15) $C_{2-5}\text{alkynyl}X^8R^{29}$ (wherein X^8 represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴C(O)-, -C(O)NR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 16) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{29}$ (wherein X⁹ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹C(O)-, -C(O)NR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
- 17) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 18) $C_{2-5}\text{alkenyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 19) $C_{2-5}\text{alkynyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20) $C_{2-5}\text{alkenyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 21) $C_{2-5}\text{alkynyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 22) $C_{1-4}\text{alkyl}R^{54}(C_{1-4}\text{alkyl})_q(X^9)_rR^{55}$ (wherein X⁹ is as defined hereinbefore, q is 0 or 1, r is 0 or 1, and R⁵⁴ and R⁵⁵ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $\text{--}(-\text{O}-)_f(C_{1-4}\text{alkyl})_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl), with the proviso that R⁵⁴ cannot be hydrogen);

-11-

and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino); or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably ring C is selected from one of the following seven moieties:



wherein Z is as defined hereinbefore but is not part of ring C, it is shown for the purpose of clarity, and wherein alternatives for the values at certain positions of the rings are indicated by the possible values separated by commas.

More preferably ring C is a thienopyrimidine ring or a phthalazine ring.

Preferably Z is -O-, -NH-, -S- or a direct bond.

More preferably Z is -O-, -NH- or -S-.

Particularly Z is -O- or -NH-, especially -O-.

Preferably Z is linked to the indole, azaindole or indazole group at the 5- or 6-positions of the indole, azaindole or indazole group.

More preferably Z is linked to the indole, azaindole or indazole group at the 5-position of the indole, azaindole or indazole group.

Preferably Z is linked to an indole group at the 5- or 6-positions of the indole group.

More preferably Z is linked to an indole group at the 5-position of the indole group.

-12-

Preferably R^b represents hydrogen, C₁₋₂alkyl, C₂₋₃alkenylaminoC₂₋₃alkyl, C₂₋₃alkynylaminoC₂₋₃alkyl or -C₂₋₄alkyl(ring A) wherein ring A is selected from piperidinyl and piperazinyl and wherein ring A may bear one or more substituents selected from C₁₋₂alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, hydroxy, cyano, cyanoC₁₋₂alkyl, C₁₋₂alkylsulphonyl and C₁₋₂alkanoyl.

5 More preferably R^b represents hydrogen, methyl, C₂₋₃alkenylaminoC₂₋₃alkyl, C₂₋₃alkynylaminoC₂₋₃alkyl or -C₂₋₃alkyl(ring A) wherein ring A is selected from 4-acetylpirerazin-1-yl, 4-methylsulphonylpiperazin-1-yl, 4-cyanopiperazin-1-yl, 4-cyanomethylpiperazin-1-yl, 4-(prop-2-en-1-yl)piperazin-1-yl, 4-(prop-2-yn-1-yl)piperazin-1-yl and 4-hydroxypiperidino.

10 Particularly R^b is hydrogen or methyl, especially hydrogen.

Advantageously R¹ represents hydrogen, oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₃alkylaminoC₁₋₄alkyl, di(C₁₋₃alkyl)aminoC₁₋₄alkyl, -C₁₋₅alkyl(ring B) wherein ring B is selected from azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, N-methylpiperazin-1-yl, N-ethylpiperazin-1-yl, morpholino and 15 thiomorpholino.

Particularly R¹ represents methyl, ethyl, trifluoromethyl or halogeno.

Especially R¹ represents methyl, fluoro, chloro or bromo, more especially methyl or fluoro.

Preferably n is an integer from 0 to 3.

20 More preferably n is 0, 1 or 2.

According to one aspect of the present invention G₁ is nitrogen and G₂, G₃, G₄ and G₅ are -CH- forming an azaindole moiety which may bear one or more substituents R¹ as defined hereinbefore.

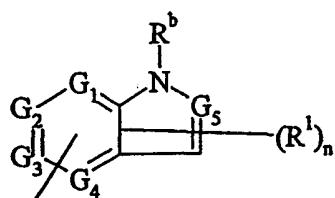
According to another aspect of the present invention G₅ is nitrogen and G₁, G₂, G₃ 25 and G₄ are -CH- forming an indazole moiety which may bear one or more substituents R¹ as defined hereinbefore.

According to another aspect of the present invention G₁, G₂, G₃, G₄ and G₅ are all -CH- forming an indole moiety which may bear one or more substituents R¹ as defined hereinbefore.

30 In one embodiment of the invention the optionally substituted indole, azaindole or indazole moiety of formula II:

-13-

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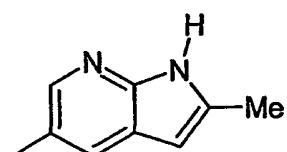
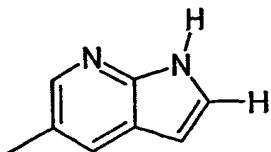
(II)

wherein R^1 , R^b , G_1 , G_2 , G_3 , G_4 and G_5 and n are as defined hereinbefore;

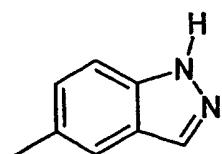
is selected from the indole moieties:

- 4-fluoro-2-methylindol-5-yl, 2-methylindol-5-yl, 2-methylindol-6-yl, 2,3-dimethylindol-5-yl,
 10 1-methylindol-5-yl, 1,2-dimethylindol-5-yl, 4-fluoroindol-5-yl, 6-fluoroindol-5-yl, indol-5-yl
 and 3-methylindol-5-yl,

the azaindole moieties:



- 15 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl and 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl,
 and the indazole moiety:

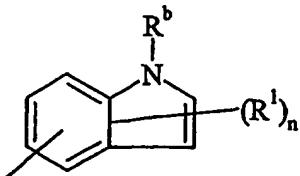


1*H*-indazol-5-yl.

- 20 The indole moieties are preferred over the azaindole and indazole moieties.

In one embodiment of the invention the optionally substituted indole moiety of formula II¹:

5



wherein R¹, R^b and n are as defined hereinbefore;

is selected from 4-fluoro-2-methylindol-5-yl, 2-methylindol-5-yl, 2-methylindol-6-yl, 2,3-

- 10 dimethylindol-5-yl, 1-methylindol-5-yl, 1,2-dimethylindol-5-yl, 4-fluoroindol-5-yl, 6-fluoroindol-5-yl and indol-5-yl.

Particularly the optionally substituted indole moiety of formula II is selected from 4-fluoro-2-methylindol-5-yl, 4-fluoroindol-5-yl and 6-fluoroindol-5-yl, more especially from 4-fluoro-2-methylindol-5-yl.

15

Preferably m is 1 or 2.

Advantageously X¹ represents a direct bond, -O-, -S-, -NR⁶C(O)-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

- 20 Preferably X¹ represents a direct bond, -O-, -S-, -NR⁶C(O)-, -NR⁹SO₂- (wherein R⁶ and R⁹ each independently represents hydrogen or C₁₋₂alkyl) or NH.

More preferably X¹ represents -O-, -S-, -NR⁶C(O)- (wherein R⁶ represents hydrogen or C₁₋₂alkyl) or NH.

- Particularly X¹ represents -O- or -NR⁶C(O)- (wherein R⁶ represents hydrogen or C₁₋₂alkyl), more particularly -O- or -NHC(O)-, especially -O-.

According to another aspect of the present invention X¹ represents -O- or a direct bond.

Advantageously X² represents -O- or NR¹² (wherein R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

- 30 Advantageously X³ represents -O-, -S-, -SO-, -SO₂-, -NR¹⁷C(O)-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

-15-

Preferably X³ represents -O-, -S-, -SO-, -SO₂- or -NR²¹- (wherein R²¹ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

More preferably X³ represents -O- or -NR²¹- (wherein R²¹ represents hydrogen or C₁₋₂alkyl).

5 According to another aspect of the present invention X³ represents -O-, -SO₂-, -NR²⁰SO₂- or -NR²¹- (wherein R²⁰ and R²¹ each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Advantageously X⁴ and X⁵ which may be the same or different each represents -O-, -S-, -SO-, -SO₂- or -NR²⁷- (wherein R²⁷ represents hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

10 Preferably X⁴ and X⁵ which may be the same or different each represents -O-, -S- or -NR²⁷- (wherein R²⁷ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

More preferably X⁴ and X⁵ which may be the same or different each represents -O- or -NH-.

Especially X⁴ and X⁵ each represents -O-.

15 Advantageously X⁶ represents -O-, -S- or -NR³⁸- (wherein R³⁸ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁶ represents -O- or -NR³⁸- (wherein R³⁸ represents hydrogen or C₁₋₂alkyl).

Especially X⁶ represents -O-.

20 Advantageously X⁷ represents -O-, -S- or -NR⁴³- (wherein R⁴³ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁷ represents -O- or -NR⁴³- (wherein R⁴³ represents hydrogen or C₁₋₂alkyl).

25 Advantageously X⁸ represents -O-, -S- or -NR⁴⁸- (wherein R⁴⁸ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁸ represents -O- or -NR⁴⁸- (wherein R⁴⁸ represents hydrogen or C₁₋₂alkyl).

Advantageously X⁹ represents -O-, -S- or -NR⁵³- (wherein R⁵³ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁹ represents -O- or -NR⁵³- (wherein R⁵³ represents hydrogen or C₁₋₂alkyl).

30 According to another aspect of the present invention X⁹ represents -O-, -CONR⁵⁰- or -NR⁵³- (wherein R⁵⁰ and R⁵³ each independently represents hydrogen or C₁₋₂alkyl).

-16-

- Conveniently R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl).
- Advantageously R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).
- In one embodiment of the present invention R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).
- Particularly R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl.
- According to another aspect of the present invention, preferably R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl.

-17-

Where R²⁹ is a 5-6-membered aromatic heterocyclic group, it preferably has 1 or 2 heteroatoms, selected from O, N and S, of which more preferably one is N, and may be substituted as hereinbefore defined.

- R²⁹ is particularly a pyridone, phenyl, pyridyl, imidazolyl, thiazolyl, thieryl,
 5 triazolyl or pyridazinyl group which group may be substituted as hereinbefore defined, more particularly a pyridone, pyridyl, imidazolyl, thiazolyl or triazolyl group, especially a pyridone, pyridyl, imidazolyl or triazolyl group which group may be substituted as hereinbefore defined.

- In one embodiment of the invention R²⁹ represents a pyridone, phenyl or 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S,
 10 which group may preferably carry up to 2 substituents, more preferably up to one substituent, selected from the group of substituents as hereinbefore defined.

- In the definition of R²⁹, conveniently substituents are selected from halogeno, C₁-alkyl, C₁₋₄alkoxy, cyano and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl,
 15 imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl).

- In the definition of R²⁹, more conveniently substituents are selected from chloro, fluoro, methyl, ethyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl,
 20 azetidinyl, morpholino and thiomorpholino).

According to another embodiment of the present invention in the definition of R²⁹, conveniently substituents are selected from halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

- Advantageously R⁵⁴ and R⁵⁵ are each independently a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl).

-18-

- Preferably R⁵⁴ and R⁵⁵ are each selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl).
- 5 3alkoxycarbonyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl).

- More preferably R⁵⁴ and R⁵⁵ are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).
- 10 3alkoxycarbonyl and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).
- 15 azetidinyl, morpholino and thiomorpholino).

- Particularly R⁵⁴ and R⁵⁵ are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).
- 20 morpholino and thiomorpholino).

- More particularly R⁵⁴ and R⁵⁵ are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group is unsubstituted.

- Conveniently R² represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following twenty-two groups:
- 1) oxiranylC₁₋₄alkyl or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C₂₋₅alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;
- 2) C₂₋₃alkylX²C(O)R¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₄alkyl or C₁₋₂alkoxyethyl));

-19-

- 3) $C_{2-4}alkylX^3R^{16}$ (wherein X^3 is as hereinbefore defined and R^{16} represents hydrogen, $C_{1-3}alkyl$, cyclopentyl, cyclohexyl or a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-3}alkoxy$ and which cyclic group 5 may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group - $(-O-)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered 10 saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}alkyl$));
- 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-3}alkyl$);
- 5) R^{28} (wherein R^{28} is as defined hereinbefore);
- 15 6) $C_{1-5}alkylR^{56}$ (wherein R^{56} is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to $C_{1-5}alkyl$ through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group - $(-O-)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered 20 saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}alkyl$)) or $C_{2-5}alkylR^{57}$ (wherein R^{57} is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, of which one is N and the other may be selected independently from O, S and N, which heterocyclic group is linked to $C_{2-5}alkyl$ through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group - $(-O-)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0

-20-

- or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 7) C₃₋₄alkenylR⁵⁸ (wherein R⁵⁸ represents R⁵⁶ or R⁵⁷ as defined hereinbefore);
- 5 8) C₃₋₄alkynylR⁵⁸ (wherein R⁵⁸ represents R⁵⁶ or R⁵⁷ as defined hereinbefore);
- 9) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 11) C₃₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 12) C₃₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 10 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
- 14) C₄₋₅alkenylX⁷R²⁹ (wherein X⁷ and R²⁹ are as defined hereinbefore);
- 15) C₄₋₅alkynylX⁸R²⁹ (wherein X⁸ and R²⁹ are as defined hereinbefore);
- 16) C₂₋₃alkylX⁹C₁₋₃alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
- 17) C₂₋₃alkylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 15 18) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 19) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino,
- 20 aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20) C₂₋₅alkenylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 21) C₂₋₅alkynylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 22) C₁₋₃alkylR⁵⁴(C₁₋₃alkyl)_q(X⁹)_rR⁵⁵ (wherein X⁹, q, r, R⁵⁴ and R⁵⁵ are as defined hereinbefore);
- 25 and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].

Advantageously R² represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following twenty-two groups:

- 30 1) C₁₋₄alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C₂₋₅alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

-21-

- 2) $C_{2-3}alkylX^2C(O)R^{11}$ (wherein X^2 is as hereinbefore defined and R^{11} represents $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13} , R^{14} and R^{15} which may be the same or different are each $C_{1-4}alkyl$ or $C_{1-2}alkoxyethyl$));
- 3) $C_{2-4}alkylX^3R^{16}$ (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from $C_{1-3}alkyl$, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl and tetrahydropyranyl, which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-2}alkoxy$ and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}cyanoalkyl$, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-3}alkoxycarbonyl$, $C_{1-3}alkylamino$, $di(C_{1-3}alkyl)amino$, $C_{1-3}alkylaminoC_{1-3}alkyl$, $di(C_{1-3}alkyl)aminoC_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, $di(C_{1-3}alkyl)aminoC_{1-3}alkoxy$ and a group $\text{(-O-)}_f(C_{1-3}alkyl)_g$ ring D (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}alkyl$));
- 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-3}alkyl$);
- 5) R^{28} (wherein R^{28} is as defined hereinbefore);
- 6) $C_{1-4}alkylR^{59}$ (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-4}alkyl$ through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}cyanoalkyl$, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkanoyl$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonyl$,
- $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-3}alkoxycarbonyl$, $C_{1-3}alkylamino$, $di(C_{1-3}alkyl)amino$, $C_{1-3}alkylaminoC_{1-3}alkyl$, $di(C_{1-3}alkyl)aminoC_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, $di(C_{1-3}alkyl)aminoC_{1-3}alkoxy$ and a group $\text{(-O-)}_f(C_{1-3}alkyl)_g$ ring D (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}alkyl$) or $C_{2-4}alkylR^{60}$ (wherein R^{60} is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}alkyl$,

-22-

- \geq cynoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkanoyl, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group $-(O)(C_{1-3}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0
- 5 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl));
- 7) C₃₋₄alkenylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);
- 8) C₃₋₄alkynylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);
- 10 9) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 10) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 11) 1-R²⁹prop-1-en-3-yl or 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹prop-1-en-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);
- 15 12) 1-R²⁹prop-1-yn-3-yl or 1-R²⁹but-2-yn-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹prop-1-yn-3-yl, R²⁹ is linked to the alkynyl group via a carbon atom);
- 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
- 14) 1-(R²⁹X⁷)but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined hereinbefore);
- 20 15) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined hereinbefore);
- 16) C₂₋₃alkylX⁹C₁₋₃alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
- 17) C₂₋₃alkylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 18) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 25 19) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 30 20) C₂₋₄alkenylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 21) C₂₋₄alkynylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and

-23-

22) $C_{1-3}alkylR^{54}(C_{1-3}alkyl)_q(X^9)_rR^{55}$ (wherein X^9 , q , r , R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any $C_{1-3}alkyl$, $C_{2-5}alkenyl$ or $C_{2-5}alkynyl$ group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino].

5 Preferably R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, $C_{1-3}alkyl$, cyano, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty groups:

- 1) $C_{1-3}alkyl$ which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or $C_{2-3}alkyl$ which may be unsubstituted or
- 10 substituted with one or more groups selected from hydroxy and amino;
- 2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl, or 2-(N-
- 15 methyl-N-(butoxycarbonyl)amino)ethyl;
- 3) $C_{2-3}alkylX^3R^{16}$ (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from $C_{1-3}alkyl$, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl and tetrahydropyranyl which group is linked to X^3 through a carbon atom and which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from hydroxy, halogeno and $C_{1-2}alkoxy$ and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl or tetrahydropyranyl group may bear one substituent selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, di($C_{1-3}alkyl$)amino, $C_{1-3}alkylaminoC_{1-3}alkyl$, di($C_{1-3}alkyl$)amino $C_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$,
- 20 di($C_{1-3}alkyl$)amino $C_{1-3}alkoxy$ and a group $\text{(-O-)}_f(C_{1-3}alkyl)_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));
- 25 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-2}alkyl$);
- 30 5) R^{28} (wherein R^{28} is as defined hereinbefore);
- 6) $C_{1-3}alkylR^{59}$ (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, imidazolidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-

- dithian-2-yl, which group is linked to C₁₋₃alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₂cyanoalkyl, C₁₋₂alkyl, C₁₋₂hydroxyalkyl, C₁₋₂alkoxy, C₁₋₂alkanoyl, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₂alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino)) or C₂₋₃alkylR⁶⁰ (wherein R⁶⁰ is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino
- 5 10 which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₂cyanoalkyl, C₁₋₂alkyl, C₁₋₂hydroxyalkyl, C₁₋₂alkoxy, C₁₋₂alkanoyl, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₂alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));
- 15 7) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 8) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 9) 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore);
- 20 10) 1-R²⁹but-2-yn-4-yl (wherein R²⁹ is as defined hereinbefore);
- 11) C₁₋₃alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
- 12) 1-(R²⁹X⁷)but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined hereinbefore);
- 13) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined hereinbefore);
- 14) C₂₋₃alkylX⁹C₁₋₃alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
- 25 15) C₂₋₃alkylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 16) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 30 17) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄

-25-

- 4alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 18) C₂₋₃alkenylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 19) C₂₋₃alkynylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 5 20) C₁₋₃alkylR⁵⁴(C₁₋₃alkyl)_q(X⁹)_rR⁵⁵ (wherein X⁹, q, r, R⁵⁴ and R⁵⁵ are as defined hereinbefore);
- and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].
- More preferably R² represents hydroxy, C₁₋₃alkyl, amino or R⁵X¹ - [wherein X¹ is as
- 10 hereinbefore defined and R⁵ represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphonyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl,
- 20 (1-methylpiperidin-4-yl)methyl, 2-(4-hydroxypiperidino)ethyl, 3-(4-hydroxypiperidino)propyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl,
- 25 cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl,
- 30 cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl,

- 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-
 5 cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-
 10 dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-
 15 ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 3-pyridylmethyl, 2-(3-pyridyl)ethyl, 3-(3-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-
 20 oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 2-(4-cyanomethylpiperazin-1-yl)ethyl, 3-(4-cyanomethylpiperazin-1-yl)propyl, 2-(4-acetyl)piperazin-1-yl)ethyl, 3-(4-acetyl)piperazin-1-yl)propyl, 2-(4-methylsulphonylpiperazin-1-yl)ethyl, 3-(4-methylsulphonylpiperazin-1-
 25 yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 2-(4-cyanomethylpiperazin-1-yl)ethyl, 3-(4-cyanomethylpiperazin-1-yl)propyl, 2-(4-acetyl)piperazin-1-yl)ethyl, 3-(4-acetyl)piperazin-1-yl)propyl, 2-(4-methylsulphonylpiperazin-1-yl)ethyl, 3-(4-methylsulphonylpiperazin-1-
 30 yl)propyl, 3-(methylsulphanyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphanyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-(N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-(N-(3-morpholinopropylsulphonyl)-

- N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 2-(1-(2-pyrrolidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-pyrrolidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-piperidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-piperidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-morpholinoethyl)piperidin-4-yl)ethyl, 2-(1-(3-morpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-thiomorpholinoethyl)piperidin-4-yl)ethyl, 2-(1-(3-thiomorpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-azetidinylethyl)piperidin-4-yl)ethyl,
- 10 15 2-(1-(3-azetidinylpropyl)piperidin-4-yl)ethyl, 3-morpholino-2-hydroxypropyl, (2R)-3-morpholino-2-hydroxypropyl, (2S)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2R)-3-piperidino-2-hydroxypropyl, (2S)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2R)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2S)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 9935 9940 9945 9950 9955 9960 9965 9970 9975 9980 9985 9990 9995 10000 10005 10010 10015 10020 10025 10030 10035 10040 10045 10050 10055 10060 10065 10070 10075 10080 10085 10090 10095 10100 10105 10110 10115 10120 10125 10130 10135 10140 10145 10150 10155 10160 10165 10170 10175 10180 10185 10190 10195 10200 10205 10210 10215 10220 10225 10230 10235 10240 10245 10250 10255 10260 10265 10270 10275 10280 10285 10290 10295 10300 10305 10310 10315 10320 10325 10330 10335 10340 10345 10350 10355 10360 10365 10370 10375 10380 10385 10390 10395 10400 10405 10410 10415 10420 10425 10430 10435 10440 10445 10450 10455 10460 10465 1

- (N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, 2-(4-hydroxypiperidino)ethyl, 3-(4-hydroxypiperidino)propyl,
- 10 (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-
- 15 (ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl,
- 20 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-
- 25 (cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-
- 30 tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-

- methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-5 (1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 3-pyridylmethyl, 2-(3-pyridyl)ethyl, 3-(3-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 10 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 2-(4-cyanomethylpiperazin-1-yl)ethyl, 3-(4-cyanomethylpiperazin-1-yl)propyl, 2-(4-acetyl)piperazin-1-yl)ethyl, 3-(4-acetyl)piperazin-1-yl)propyl, 2-(4-methylsulphonylpiperazin-1-yl)ethyl, 3-(4-methylsulphonylpiperazin-1-yl)propyl, 3-(methylsulphiny)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphiny)propyl, 3-(15 (ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-(N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-(N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-(N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-20 (tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-25 thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 2-(1-(2-pyrrolidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-pyrrolidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-piperidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-piperidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-morpholinoethyl)piperidin-4-yl)ethyl, 2-(1-(3-morpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-thiomorpholinoethyl)piperidin-4-yl)ethyl, 2-30 (1-(3-thiomorpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-azetidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-azetidinylpropyl)piperidin-4-yl)ethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-

- hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].
- 10 More particularly R² represents C₁₋₃alkyl, amino or R⁵X¹ - [wherein X¹ is as hereinbefore defined and R⁵ represents ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, 2-(4-hydroxypiperidino)ethyl, 3-(4-hydroxypiperidino)propyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl,

2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-5
5 yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-10
10 (cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-15
15 dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-20
20 pyridyl)propyl, 3-pyridylmethyl, 2-(3-pyridyl)ethyl, 3-(3-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 25
25 2-(4-cyanomethylpiperazin-1-yl)ethyl, 3-(4-cyanomethylpiperazin-1-yl)propyl, 2-(4-acetyl)piperazin-1-yl)ethyl, 3-(4-acetyl)piperazin-1-yl)propyl, 2-(4-methylsulphonylpiperazin-1-yl)ethyl, 3-(4-methylsulphonylpiperazin-1-yl)propyl, 3-(methylsulphanyl)propyl, 3-(ethylsulphanyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-(N-(3-morpholinopropyl)sulphonyl)-N-30
30 methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-

- (tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 2-(1-(2-pyrrolidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-pyrrolidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-piperidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-piperidinylpropyl)piperidin-4-yl)ethyl, 2-(1-(2-morpholinoethyl)piperidin-4-yl)ethyl, 2-(1-(3-morpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-thiomorpholinoethyl)piperidin-4-yl)ethyl, 2-(1-(3-thiomorpholinopropyl)piperidin-4-yl)ethyl, 2-(1-(2-azetidinylethyl)piperidin-4-yl)ethyl, 2-(1-(3-azetidinylpropyl)piperidin-4-yl)ethyl, 3-morpholino-2-hydroxypropyl, (2R)-3-morpholino-2-hydroxypropyl, (2S)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2R)-3-piperidino-2-hydroxypropyl, (2S)-3-piperidino-2-hydroxypropyl, 3-
- 15 pyrrolidin-1-yl-2-hydroxypropyl, (2R)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2S)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2R)-3-(N,N-diethylamino)-2-hydroxypropyl, (2S)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2R)-3-
- 20 (isopropylamino)-2-hydroxypropyl, (2S)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2R)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2S)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

In another aspect R² represents ethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypoxo, 2-25 (methylsulphonyl)ethoxy, 2-(methylsulphonyl)ethoxy, 2-(ethylsulphonyl)ethoxy, 2-(ethylsulphonyl)ethoxy, 2-(N,N-dimethylsulphamoyl)ethoxy, 2-(N-methylsulphamoyl)ethoxy, 2-sulphamoylethoxy, 2-(methylamino)ethoxy, 3-(methylamino)propoxy, 2-(ethylamino)ethoxy, 3-(ethylamino)propoxy, 2-(N,N-dimethylamino)ethoxy, 3-(N,N-dimethylamino)propoxy, 2-(N,N-diethylamino)ethoxy, 3-(N,N-diethylamino)propoxy, 2-(N-30 methyl-N-methylsulphonylamino)ethoxy, 3-(N-methyl-N-methylsulphonylamino)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-

(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(piperidin-2-yl)ethoxy, 3-(piperidin-2-yl)propoxy, (1-methylpiperidin-3-yl)methoxy, (1-methylpiperidin-4-yl)methoxy, 2-(4-hydroxypiperidino)ethoxy, 3-(4-hydroxypiperidino)propoxy, (1-cyanomethylpiperidin-3-yl)methoxy, (1-cyanomethylpiperidin-4-yl)methoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 2-(1-cyanomethylpiperidin-3-yl)ethoxy, 2-(1-cyanomethylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 3-(1-cyanomethylpiperidin-3-yl)propoxy, 3-(1-cyanomethylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, ((2-methoxyethyl)piperidin-3-yl)methoxy, 2-((2-methoxyethyl)piperidin-4-yl)methoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, (1-(2-methylsulphonylethyl)piperidin-3-yl)methoxy, (1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy, 3-(1-isopropylpiperidin-4-yl)propoxy, 2-(piperidin-4-yloxy)ethoxy, 3-(piperidin-4-yloxy)propoxy, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethoxy, 3-(1-(cyanomethyl)piperidin-4-yloxy)propoxy, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propoxy, 2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy, (pyrrolidin-2-yl)methoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (1,3-dioxolan-2-yl)methoxy, 2-(1,3-dioxolan-2-yl)ethoxy, 2-(2-methoxyethylamino)ethoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 2-(2-hydroxyethylamino)ethoxy, 3-(2-methoxyethylamino)propoxy, 3-(N-(2-methoxyethyl)-N-methylamino)propoxy, 3-(2-hydroxyethylamino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-

- (1,2,3-triazol-2-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-4-yl)ethoxy, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 4-pyridylmethoxy, 2-(4-pyridyl)ethoxy, 3-(4-pyridyl)propoxy, 3-pyridylmethoxy, 2-(3-pyridyl)ethoxy, 3-(3-pyridyl)propoxy, 2-(4-pyridyloxy)ethoxy, 2-(4-pyridylamino)ethoxy, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy, 2-(2-oxo-imidazolidin-1-yl)ethoxy, 3-(2-oxo-imidazolidin-1-yl)propoxy, 2-thiomorpholinoethoxy, 3-thiomorpholinopropoxy, 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-(4-acetyl(piperazin-1-yl)ethoxy, 3-(4-acetyl(piperazin-1-yl)propoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 3-(methylsulphanyl)propoxy, 3-(methylsulphonyl)propoxy, 3-(ethylsulphanyl)propoxy, 3-(ethylsulphonyl)propoxy, 2-(5-methyl-1,2,4-triazol-1-yl)ethoxy, 2-((N-3-morpholinopropylsulphonyl)-N-methyl)amino)ethoxy, 2-((N-methyl-N-4-pyridyl)amino)ethoxy, 3-(4-oxidomorpholino)propoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propoxy, 2-(2-morpholinoethoxy)ethoxy, 3-(2-morpholinoethoxy)propoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yloxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy, 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy, 2-(1-(2-pyrrolidinylethyl)piperidin-4-yl)ethoxy, 2-(1-(3-pyrrolidinylpropyl)piperidin-4-yl)ethoxy, 2-(1-(2-morpholinoethyl)piperidin-4-yl)ethoxy, 2-(1-(2-thiomorpholinoethyl)piperidin-4-yl)ethoxy, 2-(1-(2-azetidinylethyl)piperidin-4-yl)ethoxy, 2-(1-(3-azetidinylpropyl)piperidin-4-yl)ethoxy, 3-(2-morpholino-2-hydroxypropoxy), (2*R*)-3-morpholino-2-hydroxypropoxy, (2*S*)-3-morpholino-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, (2*R*)-3-piperidino-2-hydroxypropoxy, (2*S*)-3-piperidino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, (2*R*)-3-pyrrolidin-1-yl-

-35-

- 2-hydroxypropoxy, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, 3-(N,N-diethylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropoxy, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropoxy, 3-5 (isopropylamino)-2-hydroxypropoxy, (2*R*)-3-(isopropylamino)-2-hydroxypropoxy, (2*S*)-3-(isopropylamino)-2-hydroxypropoxy, 3-(N,N-diisopropylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy.

- According to another aspect of the present invention conveniently R² represents
- 10 hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following twenty-two groups:
 - 1) oxiranylC₁₋₄alkyl or C₁₋₅salkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C₂₋₅salkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;
 - 15 2) C₂₋₃alkylX²C(O)R¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₄alkyl or C₁₋₂alkoxyethyl));
 - 3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₃alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy and a group -(-O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
 - 25 4) C₂₋₃alkylX⁴C₂₋₃alkylX⁵R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C₁₋₃alkyl);
 - 30 5) R²⁸ (wherein R²⁸ is as defined hereinbefore);

- 6) $C_{1-5}alkylR^{56}$ (wherein R^{56} is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to $C_{1-5}alkyl$ through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group $-(O)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}alkyl$)) or $C_{2-5}alkylR^{57}$ (wherein R^{57} is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, of which one is N and the other may be selected independently from O, S and N, which heterocyclic group is linked to $C_{2-5}alkyl$ through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group $-(O)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}alkyl$));
- 7) $C_{3-4}alkenylR^{58}$ (wherein R^{58} represents R^{56} or R^{57} as defined hereinbefore);
- 8) $C_{3-4}alkynylR^{58}$ (wherein R^{58} represents R^{56} or R^{57} as defined hereinbefore);
- 9) R^{29} (wherein R^{29} is as defined hereinbefore);
- 10) $C_{1-5}alkylR^{29}$ (wherein R^{29} is as defined hereinbefore);
- 11) $C_{3-5}alkenylR^{29}$ (wherein R^{29} is as defined hereinbefore);
- 12) $C_{3-5}alkynylR^{29}$ (wherein R^{29} is as defined hereinbefore);
- 13) $C_{1-5}alkylX^6R^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);
- 14) $C_{4-5}alkenylX^7R^{29}$ (wherein X^7 and R^{29} are as defined hereinbefore);
- 15) $C_{4-5}alkynylX^8R^{29}$ (wherein X^8 and R^{29} are as defined hereinbefore);
- 16) $C_{2-3}alkylX^9C_{1-3}alkylR^{29}$ (wherein X^9 and R^{29} are as defined hereinbefore);
- 17) $C_{2-3}alkylX^9C_{1-3}alkylR^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore);

- 18) C₂-alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 19) C₂-alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 5 20) C₂₋₅alkenylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 21) C₂₋₅alkynylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 22) C₁₋₃alkylR⁵⁴(C₁₋₃alkyl)_q(X⁹)R⁵⁵ (wherein X⁹, q, r, R⁵⁴ and R⁵⁵ are as defined 10 hereinbefore);
- and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].

According to another aspect of the present invention advantageously R² represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as 15 hereinbefore defined and R⁵ is selected from one of the following twenty-two groups:

1) C₁₋₄alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C₂₋₅alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C₂₋₃alkylX²C(O)R¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents -NR¹³R¹⁴ or 20 -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₄alkyl or C₁₋₂alkoxyethyl));

3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ is a group selected from C₁₋₃alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl and tetrahydropyranyl, which C₁₋₃alkyl group may bear 1 or 2 substituents selected 25 from oxo, hydroxy, halogeno and C₁₋₂alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanooalkyl, C₁₋₃alkyl, C₁₋₃hydroxalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -30 (-O-)f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and

- thiomorpholino, which cyclic group may bear one or more substituents selected from C₁-alkyl));
- 4) C₂₋₃alkylX⁴C₂₋₃alkylX⁵R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C₁₋₃alkyl);
- 5) R²⁸ (wherein R²⁸ is as defined hereinbefore);
- 6) C₁₋₄alkylR⁵⁹ (wherein R⁵⁹ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C₁₋₄alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(-O-)f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl)) or C₂₋₄alkylR⁶⁰ (wherein R⁶⁰ is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃cyanoalkyl, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl, C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(-O-)f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C₁₋₃alkyl));
- 7) C₃₋₄alkenylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);
- 8) C₃₋₄alkynylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);
- 9) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 10) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 30 11) 1-R²⁹prop-1-en-3-yl or 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹prop-1-en-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);

- 12) $1-R^{29}\text{prop-1-yn-3-yl}$ or $1-R^{29}\text{but-2-yn-4-yl}$ (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is $1-R^{29}\text{prop-1-yn-3-yl}$, R^{29} is linked to the alkynyl group via a carbon atom);
- 13) $C_{1-5}\text{salkyl}X^6R^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);
- 5 14) $1-(R^{29}X^7)\text{but-2-en-4-yl}$ (wherein X^7 and R^{29} are as defined hereinbefore);
- 15) $1-(R^{29}X^8)\text{but-2-yn-4-yl}$ (wherein X^8 and R^{29} are as defined hereinbefore);
- 16) $C_{2-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{29}$ (wherein X^9 and R^{29} are as defined hereinbefore);
- 17) $C_{2-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore);
- 18) $C_{2-5}\text{alkenyl}$ which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-4}\text{alkylamino}$, N,N-di($C_{1-4}\text{alkyl}$)amino, aminosulphonyl, N- $C_{1-4}\text{alkylaminosulphonyl}$ and N,N-di($C_{1-4}\text{alkyl}$)aminosulphonyl;
- 10 19) $C_{2-5}\text{salkynyl}$ which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-4}\text{alkylamino}$, N,N-di($C_{1-4}\text{alkyl}$)amino, aminosulphonyl, N- $C_{1-4}\text{alkylaminosulphonyl}$ and N,N-di($C_{1-4}\text{alkyl}$)aminosulphonyl;
- 15 20) $C_{2-4}\text{alkenyl}X^9C_{1-3}\text{alkyl}R^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore);
- 21) $C_{2-4}\text{alkynyl}X^9C_{1-3}\text{alkyl}R^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore); and
- 22) $C_{1-3}\text{alkyl}R^{54}(C_{1-3}\text{alkyl})_q(X^9)_rR^{55}$ (wherein X^9 , q , r , R^{54} and R^{55} are as defined hereinbefore);
- 20 and additionally wherein any $C_{1-5}\text{alkyl}$, $C_{2-5}\text{alkenyl}$ or $C_{2-5}\text{salkynyl}$ group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino].

According to another aspect of the present invention preferably R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, $C_{1-3}\text{alkyl}$, cyano, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty groups:

1) $C_{1-3}\text{alkyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or $C_{2-3}\text{alkyl}$ which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-

- methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl, or 2-(N-methyl-N-(butoxycarbonyl)amino)ethyl;
- 3) $C_{2-3}alkylX^3R^{16}$ (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from $C_{1-3}alkyl$, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl,
- 5 imidazolidinyl and tetrahydropyranyl which group is linked to X^3 through a carbon atom and which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from hydroxy, halogeno and $C_{1-2}alkoxy$ and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl or tetrahydropyranyl group may bear one substituent selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, di($C_{1-3}alkyl$)amino, $C_{1-3}alkylaminoC_{1-3}alkyl$, di($C_{1-3}alkyl$)amino $C_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, di($C_{1-3}alkyl$)amino $C_{1-3}alkoxy$ and a group $-(O)_f(C_{1-3}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));
- 10 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-2}alkyl$);
- 5) R^{28} (wherein R^{28} is as defined hereinbefore);
- 6) $C_{1-3}alkylR^{59}$ (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, imidazolidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-
- 20 dithian-2-yl, which group is linked to $C_{1-3}alkyl$ through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, di($C_{1-3}alkyl$)amino, $C_{1-3}alkylaminoC_{1-3}alkyl$, di($C_{1-3}alkyl$)amino $C_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, di($C_{1-3}alkyl$)amino $C_{1-3}alkoxy$ and a group -
- 25 $-(O)_f(C_{1-3}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino)) or $C_{2-3}alkylR^{60}$ (wherein R^{60} is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, di($C_{1-3}alkyl$)amino, $C_{1-3}alkylaminoC_{1-3}alkyl$, di($C_{1-3}alkyl$)amino $C_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, di($C_{1-3}alkyl$)amino $C_{1-3}alkoxy$ and a group -

-41-

- (-O-)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));
- 7) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 5 8) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 9) 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore);
- 10) 1-R²⁹but-2-yn-4-yl (wherein R²⁹ is as defined hereinbefore);
- 11) C₁₋₃alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
- 12) 1-(R²⁹X⁷)but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined hereinbefore);
- 10 13) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined hereinbefore);
- 14) C₂₋₃alkylIX⁹C₁₋₃alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
- 15) C₂₋₃alkylIX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 16) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 17) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20 21) di(C₁₋₄alkyl)aminosulphonyl;
- 18) C₂₋₃alkenylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
- 19) C₂₋₃alkynylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
- 20) C₁₋₃alkylR⁵⁴(C₁₋₃alkyl)_q(X⁹)_rR⁵⁵ (wherein X⁹, q, r, R⁵⁴ and R⁵⁵ are as defined hereinbefore);
- 25 and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].
- According to another aspect of the present invention more preferably R² represents hydroxy, C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 30 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoyleethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl,

-42-

- 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-
- 5 (methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-
- 10 10)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-
- 15 15)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-
- 20 20)methylsulphonyl)ethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonyl)ethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethyl, 2-(2-methylsulphonyl)ethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-
- 25 25)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-
- 30 30)(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-

- dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-5 methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-10 imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphonyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-(N-(1-15 methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-(N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-(N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-(2-20 (pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinyethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinyethyl)piperidin-4-ylmethyl, 1-(2-piperidinyethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl or 1-(3-25 azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-

hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

- According to another aspect of the present invention particularly R² represents C₁.
- 5 3alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ represents ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-
 - 10 (ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-
 - 15 (ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl,
 - 20 (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-
 - 25 (ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-
 - 30 yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-

- isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-5 (cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-10 dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-15 ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-20 thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphonyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-(N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-(N-(3-morpholinopropylsulphonyl)-25 N-methyl)amino)ethyl, 2-(N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 30 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-

- thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl or 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-
- 5 hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-
- 10 hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

- According to another aspect of the present invention more particularly R² represents C₁₋₃alkyl, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ represents ethyl,
- 15 trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-
- 20 diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-
- 25 methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-
- 30 cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-

yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-
isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-cyanoethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(
piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphanyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphanyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl,
morpholino, 2-(N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-(N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-

- (2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl or 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-
- 5 piperidin-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-
- 10 hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

In another aspect R² represents ethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-

- 20 hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-(methylsulphinyl)ethoxy, 2-(methylsulphonyl)ethoxy, 2-(ethylsulphinyl)ethoxy, 2-(ethylsulphonyl)ethoxy, 2-(N,N-dimethylsulphamoyl)ethoxy, 2-(N-methylsulphamoyl)ethoxy, 2-sulphamoylethoxy, 2-(methylamino)ethoxy, 3-(methylamino)propoxy, 2-(ethylamino)ethoxy, 3-(ethylamino)propoxy, 2-(N,N-dimethylamino)ethoxy, 3-(N,N-dimethylamino)propoxy, 2-(N-methyl-N-methylsulphonylamino)ethoxy, 3-(N-methyl-N-methylsulphonylamino)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-(piperidin-3-ylmethoxy), piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-
- 25
- 30

-49-

- yl)propoxy, 2-(piperidin-2-yl)ethoxy, 3-(piperidin-2-yl)propoxy, (1-methylpiperidin-3-yl)methoxy, (1-methylpiperidin-4-yl)methoxy, (1-cyanomethylpiperidin-3-yl)methoxy, (1-cyanomethylpiperidin-4-yl)methoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 2-(1-cyanomethylpiperidin-3-yl)ethoxy, 2-(1-cyanomethylpiperidin-4-yl)ethoxy, 3-5 (methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 3-(1-cyanomethylpiperidin-3-yl)propoxy, 3-(1-cyanomethylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, ((2-methoxyethyl)piperidin-3-yl)methoxy, ((2-methoxyethyl)piperidin-4-yl)methoxy, 2-((2-10 methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, (1-(2-methylsulphonylethyl)piperidin-3-yl)methoxy, (1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-15 yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy, 3-(1-isopropylpiperidin-4-yl)propoxy, 2-(piperidin-4-yloxy)ethoxy, 3-(piperidin-4-yloxy)propoxy, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethoxy, 3-(1-(cyanomethyl)piperidin-4-20 yloxy)propoxy, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propoxy, 2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy, (pyrrolidin-2-yl)methoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (1,3-dioxolan-2-yl)methoxy, 2-(1,3-dioxolan-2-yl)ethoxy, 2-(2-methoxyethylamino)ethoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 25 2-(2-hydroxyethylamino)ethoxy, 3-(2-methoxyethylamino)propoxy, 3-(N-(2-methoxyethyl)-N-methylamino)propoxy, 3-(2-hydroxyethylamino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,3-triazol-2-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-4-yl)ethoxy, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 4-pyridylmethoxy, 2-(4-pyridyl)ethoxy, 3-(4-pyridyl)propoxy, 2-(4-pyridyloxy)ethoxy, 2-(4-pyridylamino)ethoxy, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy, 2-(2-oxo-imidazolidin-1-yl)ethoxy, 3-(2-oxo-imidazolidin-1-yl)propoxy, 2-thiomorpholinethoxy, 3-thiomorpholinopropoxy, 2-(1,1-dioxothiomorpholino)ethoxy, 3-

- (1,1-dioxothiomorpholino)propoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(methylsulphanyl)propoxy, 3-(methylsulphonyl)propoxy, 3-(ethylsulphanyl)propoxy, 3-(ethylsulphonyl)propoxy, 2-(5-methyl-1,2,4-triazol-1-yl)ethoxy, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethoxy, 2-((N-methyl-N-4-pyridyl)amino)ethoxy, 3-(4-oxidomorpholino)propoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propoxy, 2-(2-morpholinoethoxy)ethoxy, 3-(2-morpholinoethoxy)propoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yloxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy or 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy, 3-morpholino-2-hydroxypropoxy, (2*R*)-3-morpholino-2-hydroxypropoxy, (2*S*)-3-morpholino-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, (2*R*)-3-piperidino-2-hydroxypropoxy, (2*S*)-3-piperidino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropoxy, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, 3-(N,N-diethylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropoxy, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropoxy, 3-(isopropylamino)-2-hydroxypropoxy, (2*R*)-3-(isopropylamino)-2-hydroxypropoxy, (2*S*)-3-(isopropylamino)-2-hydroxypropoxy, 3-(N,N-diisopropylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy.

Where one of the R² substituents is R⁵X¹- the substituent R⁵X¹- is preferably at the position of ring C which would correspond to either the 6- or 7-position of a 10-membered bicyclic moiety which is attached to Z at the 4-position.

- In another aspect of the present invention there is provided the use of compounds of the formula I, as defined hereinbefore with the proviso that Z is-O-, or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use

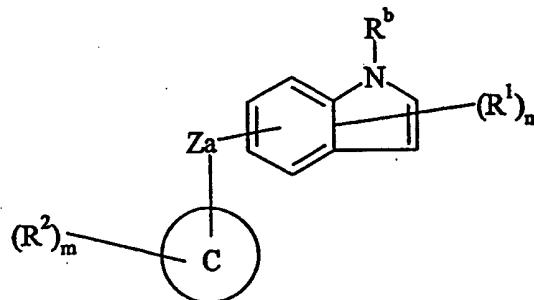
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in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

In another aspect of the present invention there is provided the use of compounds of the formula Ia:

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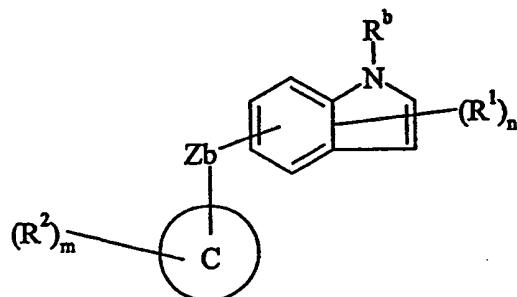


(Ia)

15 wherein ring C, R^b, R¹, R², m and n are as defined hereinbefore and Za represents -O-, -CH₂-, -NH- or -S-; or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

20 In another aspect of the present invention there is provided the use of compounds of the formula Ib:

25



(Ib)

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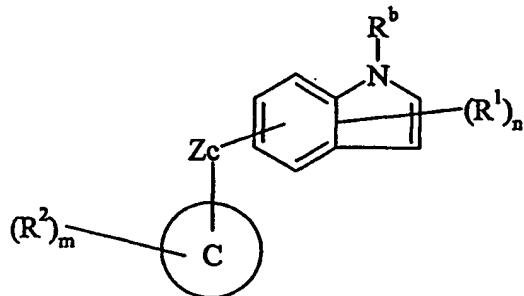
wherein ring C, R^b, R¹, R², m and n are as defined hereinbefore and Zb represents -O-,

-52-

-NH- or -S-; or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

In another aspect of the present invention there is provided the use of compounds of
5 the formula Ic:

10



(Ic)

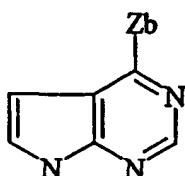
15

wherein ring C, R^b, R¹, R², m and n are as defined hereinbefore and Zc represents -O-; or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

20

In another aspect of the present invention there is provided the use of compounds of the formula Ib as defined hereinbefore with the proviso that when ring C is

25



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wherein Zb is as defined hereinbefore, (but Zb is not a part of ring C, it is shown for the purposes of clarity), at least one R² does not have a value selected from hydrogen, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and NR^cR^d (wherein each of R^c and R^d independently represents

-53-

hydrogen, C₁₋₄alkyl or phenyl which phenyl may bear 1-3 substituents selected from halogeno, trifluoromethyl, C₁₋₄alkyl and C₁₋₄alkoxy); or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as

5 humans.

According to another aspect of the present invention there is provided a compound of the formula I as defined hereinbefore and salts thereof, and prodrugs thereof for example esters and amides.

According to another aspect of the present invention there is provided a compound
10 of the formula I as defined hereinbefore and salts thereof, and prodrugs thereof for example esters and amides with the proviso that Z is -O-.

According to another aspect of the present invention there is provided a compound of the formula I¹ as defined hereinbefore and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

15 According to another aspect of the present invention there is provided a compound of the formula Ia as defined hereinbefore and salts thereof, and prodrugs thereof for example esters and amides.

According to another aspect of the present invention there is provided a compound
20 of the formula Ib as defined hereinbefore and salts thereof, and prodrugs thereof for example esters and amides.

According to another aspect of the present invention there is provided a compound of the formula Ic as defined hereinbefore and salts thereof, and prodrugs thereof for example esters and amides.

According to another aspect of the present invention there is provided a compound
25 of the formula Ib as defined hereinbefore with the proviso that if Z is -NH- then:
at least one R² is not selected from hydrogen, chloro, bromo, methyl, phenyl(hydroxymethyl), dimethylamino, methylsulphonyl, methylsulphinyl, methylsulphonyl and hydroxycyclohexylamino;
X¹ is not selected from -CH₂-, a direct bond and -C(O)NR⁷-; and
30 where R² is a group R⁵-X¹ and X¹ is -NR⁶C(O)- or -NR⁹SO₂-, R⁵ does not contain an alkenyl or alkynyl moiety;
and salts thereof, and prodrugs thereof for example esters and amides.

According to another aspect of the present invention there is provided a compound of the formula Ib as defined hereinbefore with the proviso that if Z is -NH- then:
at least one R² is not selected from hydrogen, chloro, bromo, methyl, phenyl(hydroxymethyl), dimethylamino, methylsulphonyl, methylsulphanyl, methylsulphiny, methylsulphonyl and

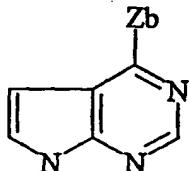
5 hydroxycyclohexylamino;

X¹ is not selected from -CH₂-; a direct bond and -C(O)NR⁷-; and

where R² is a group R⁵-X¹ and X¹ is -NR⁶C(O)- or -NR⁹SO₂-; R⁵ does not contain an alkenyl or alkynyl moiety;

and with the further proviso that when ring C is

10



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wherein Zb is as defined hereinbefore, (but Zb is not a part of ring C, it is shown for the purposes of clarity), at least one R² does not have a value selected from hydrogen, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and NR^cR^d (wherein each of R^c and R^d independently represents hydrogen, C₁₋₄alkyl or phenyl which phenyl may bear 1-3 substituents selected from halogeno,

20 trifluoromethyl, C₁₋₄alkyl and C₁₋₄alkoxy);

and salts thereof, and prodrugs thereof for example esters and amides.

According to one aspect of the present invention preferred examples are:

1-(4-fluoroindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine,

1-(indol-6-yloxy)-4-(4-pyridylmethyl)phthalazine,

25 1-(2-methylindol-6-yloxy)-4-(4-pyridylmethyl)phthalazine,

4-(4-fluoro-2-methylindol-5-yloxy)thieno[3,2-d]pyrimidine and

1-(4-fluoro-2-methylindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine,

and salts thereof.

In another aspect preferred compounds of the present invention are

30 4-(4-fluoro-2-methylindol-5-yloxy)thieno[3,2-d]pyrimidine and

1-(4-fluoro-2-methylindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine

and salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

- 5 In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated 10 otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C₆₋₁₀ aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is 15 as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C₂alkanoyl is ethanoyl and refers to CH₃C=O, C₁alkanoyl is formyl and refers to CHO. In this specification unless stated 20 otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-but enyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to 25 individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. Unless stated otherwise the term "haloalkyl" refers to an alkyl group as defined hereinbefore which bears one or more halogeno groups, such as for example trifluoromethyl.
- 30 For the avoidance of any doubt, where R² has a value of substituted or unsubstituted C₁₋₅alkyl, R² has been selected from C₁₋₃alkyl or from a group R⁵X¹ wherein X¹ is a direct

-56-

bond or -CH₂- and R⁵ is C₁-alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings 5 within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the 10 specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention 15 encompasses any chiral form (including both pure enantiomers, scalemic and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity. It is further 20 to be understood that in the names of chiral compounds (R,S) denotes any scalemic or racemic mixture while (R) and (S) denote the enantiomers. In the absence of (R,S), (R) or (S) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains R and S enantiomers in any relative proportions and a racemic mixture contains R and S enantiomers in the ration 50:50.

25 It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X¹ is, for example, a 30 group of formula -NR⁶C(O)-, it is the nitrogen atom bearing the R⁶ group which is attached to ring C and the carbonyl (C(O)) group is attached to R⁵, whereas when X¹ is, for example, a group of formula -C(O)NR⁷-, it is the carbonyl group which is attached to ring C and the

-57-

nitrogen atom bearing the R⁷ group is attached to R⁵. A similar convention applies to the other two atom X¹ linking groups such as -NR⁹SO₂- and -SO₂NR⁸- . When X¹ is -NR¹⁰- it is the nitrogen atom bearing the R¹⁰ group which is linked to ring C and to R⁵. An analogous convention applies to other groups. It is further to be understood that when X¹ represents -

5 NR¹⁰- and R¹⁰ is C₁₋₃alkoxyC₂₋₃alkyl it is the C₂₋₃alkyl moiety which is linked to the nitrogen atom of X¹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R⁵ is, for example, a group of formula C₁₋₃alkylX⁹C₁₋₃alkylR²⁹, it is the terminal C₁₋₃alkyl moiety which is linked to X¹, similarly when R⁵ is, for example, a group of

10 formula C₂₋₅alkenylR²⁸ it is the C₂₋₅alkenyl moiety which is linked to X¹ and an analogous convention applies to other groups. When R⁵ is a group 1-R²⁹prop-1-en-3-yl it is the first carbon to which the group R²⁹ is attached and it is the third carbon which is linked to X¹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the

15 formula I when R⁵ is, for example, R²⁸ and R²⁸ is a pyrrolidinyl ring which bears a group -(O-)(C₁₋₄alkyl)_gringD, it is the -O- or C₁₋₄alkyl which is linked to the pyrrolidinyl ring, unless f and g are both 0 when it is ring D which is linked to the pyrrolidinyl ring and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R²⁹ carries a C₁₋₄aminoalkyl substituent it is the C₁₋₄alkyl moiety which is attached to R²⁹ whereas when R²⁹ carries a C₁₋₄alkylamino substituent it is the amino moiety which is attached to R²⁹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R²⁸ carries a C₁₋₄alkoxyC₁₋₄alkyl substituent it is the C₁₋₄alkyl moiety which is attached to R²⁸ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R¹ is -C₁₋₅alkyl(ring B) it is the alkyl chain which is linked to the indole group and ring B is attached to the alkyl chain and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^b is C₂₋₅alkenylaminoC₁₋₄alkyl, it is the C₁₋₄alkyl group which is linked to the nitrogen atom of the 5-membered ring and an analogous convention applies to other groups.

-58-

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in International Patent Application Publication No. WO 00/47212 (Application No. PCT/GB00/00373). Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

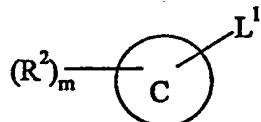
Thus, the following processes (a) to (f) and (i) to (vi) constitute further features of the present invention.

-59-

Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:

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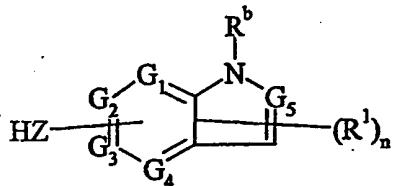


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(III)

(wherein ring C, R² and m are as defined hereinbefore and L¹ is a displaceable moiety), with a compound of the formula IV:

15



20

(IV)

(wherein R^b, R¹, G₁, G₂, G₃, G₄, G₅, Z and n are as defined hereinbefore) to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L¹ is, for example, a halogeno, alkoxy (preferably C₁₋₄alkoxy), aryloxy, alkylsulphonyl, arylsulphonyl, alkoxyalkylsulphonyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphonyl, 2-methoxyethylsulphonyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of a base. When Z is -O- such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or 30 diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

-60-

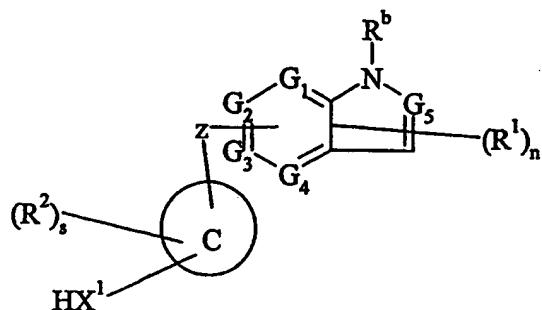
Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethyl sulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 110°C.

When Z is -NH- the reaction is advantageously effected in the presence of either an acid or a base. Such an acid is for example, an anhydrous inorganic acid such as hydrochloric acid, in the presence of a protic solvent or diluent, for example an alcohol or ester such as methanol, ethanol, 2-propanol, 2-pentanol.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Production of those compounds of formula I and salts thereof wherein at least one R² is R⁵X¹ wherein R⁵ is as defined hereinbefore and X¹ is -O-, -S-, -OC(O)- or -NR¹⁰- (wherein R¹⁰ independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) can be achieved by the reaction, conveniently in the presence of a base (as defined hereinbefore in process (a)) of a compound of the formula V:

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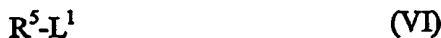


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(V)

-61-

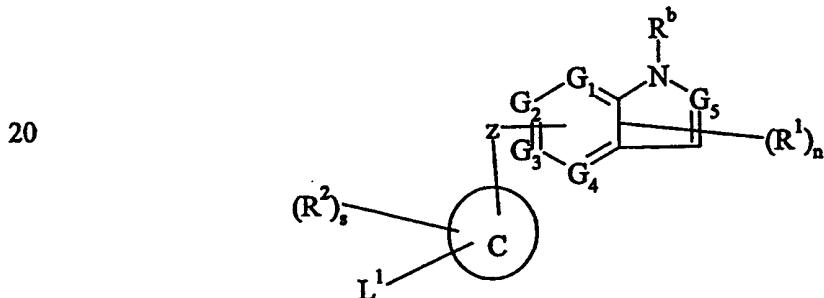
(wherein ring C, R^b, Z, G₁, G₂, G₃, G₄, G₅, R¹, R² and n are as hereinbefore defined and X¹ is as hereinbefore defined in this section and s is 0 or 1) with a compound of formula VI:



5

(wherein R⁵ and L¹ are as hereinbefore defined), L¹ is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group, or L¹ may be generated in situ from an alcohol under standard Mitsunobu conditions ("Organic Reactions", John Wiley & Sons Inc, 1992, vol 42, chapter 2, David L Hughes). The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

(c) Compounds of the formula I and salts thereof wherein at least one R² is R⁵X¹ 15 wherein R⁵ is as defined hereinbefore and X¹ is -O-, -S-, -OC(O)- or -NR¹⁰- (wherein R¹⁰ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) may be prepared by the reaction of a compound of the formula VII:



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(VII)

with a compound of the formula VIII:



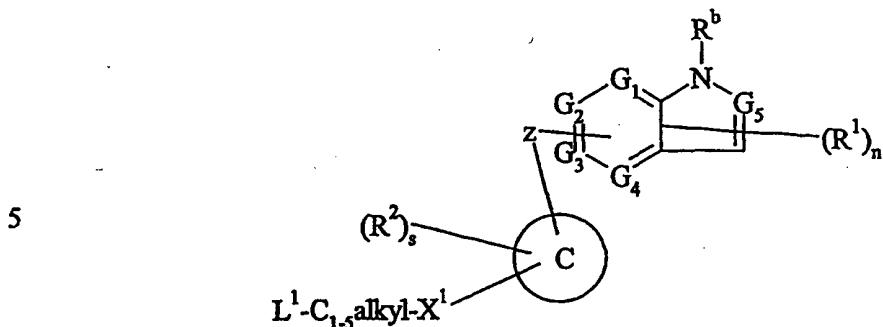
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(wherein ring C, L¹, R^b, R¹, R², R⁵, Z, G₁, G₂, G₃, G₄, G₅, n and s are all as hereinbefore defined and X¹ is as hereinbefore defined in this section). The reaction may conveniently be

effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

- 5 (d) Compounds of the formula I and salts thereof wherein at least one R² is R⁵X¹ wherein X¹ is as defined hereinbefore and R⁵ is C₁₋₅alkylR⁶², wherein R⁶² is selected from one of the following nine groups:
- 1) X¹⁰C₁₋₃alkyl (wherein X¹⁰ represents -O-, -S-, -SO₂-, -NR⁶³C(O)- or -NR⁶⁴SO₂- (wherein R⁶³ and R⁶⁴ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
 - 2) NR⁶⁵R⁶⁶ (wherein R⁶⁵ and R⁶⁶ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
 - 3) X¹¹C₁₋₅alkylX⁵R²² (wherein X¹¹ represents -O-, -S-, -SO₂-, -NR⁶⁷C(O)-, -NR⁶⁸SO₂- or -NR⁶⁹- (wherein R⁶⁷, R⁶⁸, and R⁶⁹ which may be the same or different are each hydrogen, C₁₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and X⁵ and R²² are as defined hereinbefore);
 - 4) R²⁸ (wherein R²⁸ is as defined hereinbefore);
 - 5) X¹²R²⁹ (wherein X¹² represents -O-, -S-, -SO₂-, -NR⁷⁰C(O)-, -NR⁷¹SO₂- or -NR⁷²- (wherein R⁷⁰, R⁷¹, and R⁷² which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore); and
 - 20 6) X¹³C₁₋₃alkylR²⁹ (wherein X¹³ represents -O-, -S-, -SO₂-, -NR⁷³C(O)-, -NR⁷⁴SO₂- or -NR⁷⁵- (wherein R⁷³, R⁷⁴ and R⁷⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);
 - 7) R²⁹ (wherein R²⁹ is as defined hereinbefore);
 - 8) X¹³C₁₋₄alkylR²⁸ (wherein X¹³ and R²⁸ are as defined hereinbefore); and
 - 25 9) R⁵⁴(C₁₋₄alkyl)_q(X⁹)_rR⁵⁵ (wherein q, r, X⁹, R⁵⁴ and R⁵⁵ are as defined hereinbefore); may be prepared by reacting a compound of the formula IX:

-63-



(IX)

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(wherein ring C, L¹, X¹, R^b, R¹, R², G₁, G₂, G₃, G₄, G₅, Z, n and s are as hereinbefore defined)
with a compound of the formula X:



- 15 (wherein R⁶² is as defined hereinbefore) to give a compound of the formula I or salt thereof. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C, conveniently at about 50°C.
- 20 Processes (a) and (b) are preferred over processes (c) and (d).
Process (a) is preferred over processes (b), (c) and (d).
- (e) The production of those compounds of the formula I and salts thereof wherein one or more of the substituents (R²)_m is represented by -NR⁷⁶R⁷⁷, where one (and the other is hydrogen) or both of R⁷⁶ and R⁷⁷ are C₁₋₃alkyl, may be effected by the reaction of compounds of formula I wherein the substituent (R²)_m is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are C₁₋₃alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C₁₋₃alkyl halides for example C₁₋₃alkyl chloride, bromide or iodide. The reaction is preferably effected in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature. The production of compounds of formula I and salts thereof wherein one or more of the substituents R² is an

-64-

- amino group may be effected by the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of ring C is/are a nitro group(s). The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by the hydrogenation of
- 5 a solution of the nitro compound in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating the
- 10 nitro compound and the activated metal in the presence of a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, to a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

Where the reduction is effected in the presence of activated iron, this is advantageously produced *in situ*, conveniently by the use of iron, generally iron powder, in the

15 presence of acetic acid/water and preferably at about 100°C. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of ring C is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-d) and (i-v) using a compound selected from the compounds of the formulae (I-XVII) in which the substituent(s) at the corresponding position(s) of ring C is/are

20 a nitro group(s).

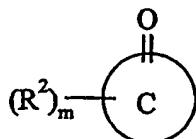
25 (f) Compounds of the formula I and salts thereof wherein X¹ is -SO- or -SO₂- may be

prepared by oxidation from the corresponding compound in which X¹ is -S- or -SO- (when X¹ is -SO₂- is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

25 Synthesis of Intermediates

(i) The compounds of formula III and salts thereof in which L¹ is halogeno may for example be prepared by halogenating a compound of the formula XI:

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(XI)

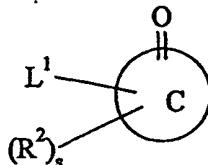
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wherein ring C, R² and m are as hereinbefore defined.

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxygenchloride and phosphorus(V)chloride.

The halogenation reaction may be effected in the presence of an inert solvent or diluent such 5 as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene, or the reaction may be effected without the presence of a solvent. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

The compounds of formula XI and salts thereof may, for example, be prepared by
10 reacting a compound of the formula XII:



15

(XII)

(wherein ring C, R², s and L¹ are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert 20 solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 110°C.

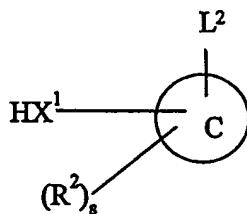
The compounds of formula XI and XII and salts thereof may be prepared by any of the methods known in the art of heterocyclic organic chemistry.

The compounds of formula III and salts thereof wherein at least one R² is R⁵X¹ and
25 wherein X¹ is -O-, -S-, -SO₂-, -OC(O)-, -C(O)NR⁷-, -SO₂NR⁸- or -NR¹⁰- (wherein R⁷, R⁸ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), may also be prepared for example by reacting a compound of the formula XIII:

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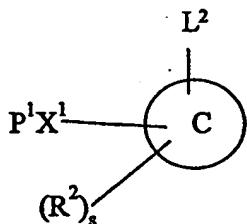


(XIII)

- (wherein ring C, R^2 and s are as hereinbefore defined, X^1 is as hereinbefore defined in this section and L^2 represents a displaceable protecting moiety) with a compound of the formula VI as hereinbefore defined, whereby to obtain a compound of formula III in which L^1 is represented by L^2 .

A compound of formula XIII is conveniently used in which L^2 represents a chloro group or a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula XIII and salts thereof may for example be prepared by deprotecting a compound of the formula XIV:



20

(XIV)

- (wherein ring C, R^2 , s and L^2 are as hereinbefore defined, P^1 is a protecting group and X^1 is as hereinbefore defined in the section describing compounds of the formula XIII). The choice of protecting group P^1 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M. Wuts, 2nd Ed. Wiley 1991, including N-sulphonyl derivatives (for example, p-toluenesulphonyl), carbamates (for example, t-butyl carbonyl), N-alkyl derivatives (for example, 2-chloroethyl, benzyl) and amino acetal derivatives (for example benzyloxymethyl).

The removal of such a protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. Deprotection may be effected by techniques well known in the literature, for example where P¹ represents a benzyl group

5 deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

One compound of formula III may if desired be converted into another compound of formula III in which the moiety L¹ is different. Thus for example a compound of formula III in which L¹ is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L¹ is halogeno by hydrolysis of a compound

10 of formula III (in which L¹ is other than halogeno) to yield a compound of formula XI as hereinbefore defined, followed by introduction of halide to the compound of formula XI, thus obtained as hereinbefore defined, to yield a compound of formula III in which L¹ represents halogen.

(ii) Compounds of formula IV may be prepared by any of the methods known in the art, such as for example those described in "Indoles Part I", "Indoles Part II", 1972 John Wiley & Sons Ltd and "Indoles Part III" 1979, John Wiley & Sons Ltd, edited by W. J. Houlihan. Compounds of formula IV may be prepared by any of the methods described in the Examples hereinafter.

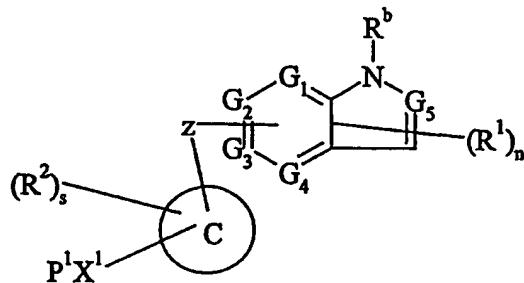
Compounds of formula IV may be prepared by any of the processes described in International Patent Application Publication No. WO 00/47212, the entire content of which is included herein by reference, with particular reference to the processes described in WO 00/47212 in Examples 48, 182 237, 242, 250 and 291 therein.

For example the azaindole 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-ol, may be prepared according to the method described in Reference Example 1 hereinafter.

25 (iii) Compounds of formula V as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XV:

-68-

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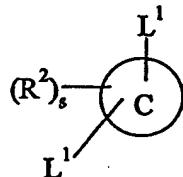


(XV)

(wherein ring C, R^b, Z, G₁, G₂, G₃, G₄, G₅, R¹, R², P¹, n and s are as hereinbefore defined and X¹ is as hereinbefore defined in the section describing compounds of the formula V) by a
10 process for example as described in (i) above.

Compounds of the formula XV and salts thereof may be made by reacting compounds of the formulae XIV and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XV or salt thereof.

(iv) Compounds of the formula VII and salts thereof may be made by reacting a
15 compound of the formula XVI:



20

(XVI)

(wherein ring C, R², s and each L¹ are as hereinbefore defined and the L¹ in the 4-position and the other L¹ in a further position on ring C may be the same or different) with a compound of the formula IV as hereinbefore defined, the reaction for example being effected by a process
25 as described in (a) above.

(v) Compounds of formula IX as defined hereinbefore and salts thereof may for example be made by the reaction of compounds of formula V as defined hereinbefore with compounds of the formula XVII:

30

L¹-C_{1,5}alkyl-L¹ (XVII)

(wherein L¹ is as hereinbefore defined) to give compounds of formula IX or salts thereof. The reaction may be effected for example by a process as described in (b) above.

(vi) Intermediate compounds wherein X¹ is -SO- or -SO₂- may be prepared by oxidation from the corresponding compound in which X¹ is -S- or -SO- (when X¹ is -SO₂- is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

10 Many of the intermediates defined herein, for example, those of the formulae IV, V, VII, IX and XV are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

15 The identification of compounds which potently inhibit the tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

20 This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic 25 domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and 30 cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant

-70-

- construct was co-transfected into insect cells (for example *Spodoptera frugiperda* 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989,
- 5 Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, *Baculovirus Expression Vectors - A Laboratory Manual*, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399
- 10 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS)

- 15 (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-bis(β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared
- 20 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1
- 25 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

- On the day before the assay 100µl of diluted substrate solution was dispensed into
- 30 all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

-71-

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25 μ l of 5 diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM manganese(II)chloride containing 8 μ M adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50 μ l of freshly diluted enzyme was added to each well and the plates were 10 incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the 15 wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) 20 solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of the "total" control wells, measured at 25 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro HUVEC Proliferation Assay

30 This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

-72-

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3 μ g/ml heparin + 1 μ g/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates.

After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 5 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO₂. On day 4 the cultures were pulsed with 1 μ Ci/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, 10 was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Solid Tumour Disease Model

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss 15 nu/nu mice, by subcutaneous injection of 1x10⁶ CaLu-6 cells/mouse in 100 μ l of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice were allocated to groups of 8-10, so as to achieve comparable group mean volumes. Tumours were measured using vernier calipers and volumes were calculated as: (l x w) x $\sqrt{(l \times w)} \times (\pi/6)$, where l is the longest diameter and w the diameter perpendicular to the longest. Test 20 compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumours were measured twice weekly. The level of growth inhibition was calculated by comparison of the mean tumour volume of the control group versus the treatment group using a Student T test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment was considered significant when p<0.05.

25 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a 30 tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as

-73-

a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a 5 unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

10 According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or 15 their ability to cause a reduction in vascular permeability.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded 20 animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

25 According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

30 As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily

dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

- 5 The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice
- 10 to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:
- 15 (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxine, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate), and in International Patent Application Publication No. WO 00/40529 the entire disclosure of which document is incorporated herein by reference);
20 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors
25 (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator
30 receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include

growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate,

- 5 fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotapec); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed); and additional types of chemotherapeutic agent include:
- 10 15 (iv) biological response modifiers (for example interferon); and
(v) antibodies (for example edrecolomab).

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate

20 (Example 1 of WO 99/02166).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such 25 compounds of the invention are expected to inhibit the growth of those primary and recurrent 30 solid tumours which are associated with VEGF, especially those tumours which are

significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the 5 development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

10 The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporation were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

15 (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

20 (iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus.

25 (vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

30 (vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) HPLC were run under 2 different conditions:

-77-

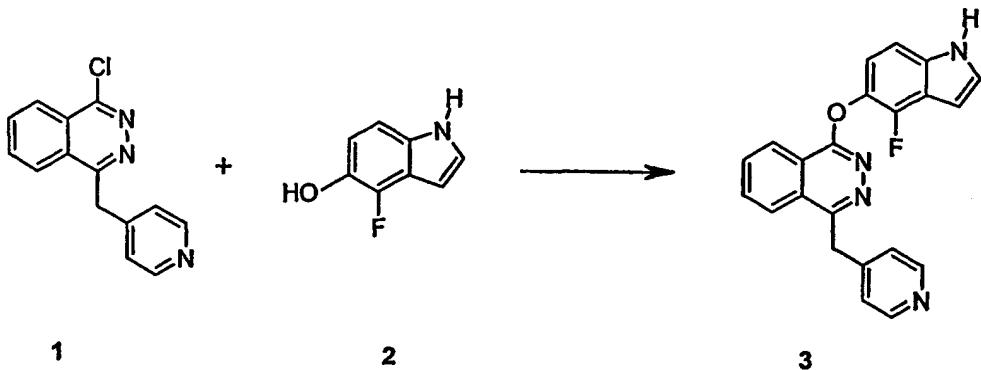
- 1) on a TSK Gel super ODS 2 μ M 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 20 to 100% in 5 minutes. Flow rate 1.4 ml/minute.
Detection: U.V. at 254 nm and light scattering detections;
- 2) on a TSK Gel super ODS 2 μ M 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 0 to 100% in 7 minutes. Flow rate 1.4 ml/minute.
Detection: U.V. at 254 nm and light scattering detections.
 - (ix) petroleum ether refers to that fraction boiling between 40-60°C
 - (x) the following abbreviations have been used:-

10	DMF <u>N,N</u> -dimethylformamide
	DMSO dimethylsulphoxide
	TFA trifluoroacetic acid
	NMP 1-methyl-2-pyrrolidinone
	THF tetrahydrofuran
15	HMDS 1,1,1,3,3,3-hexamethyldisilazane.
	HPLC RT HPLC retention time
	DEAD diethyl azodicarboxylate
	DMA dimethylacetamide
	DMAP 4-dimethylaminopyridine

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Example 1

Under nitrogen a suspension of 1-chloro-4-(4-pyridylmethyl)phthalazine (150 mg, 0.58 mmol), (J. Med. Chem. 2000, 43, 2310-2323), 4-fluoro-5-hydroxyindole (106 mg, 0.7 mmol) and cesium carbonate (306 mg, 0.938 mmol) in DMF (5.5 ml) was heated at 95°C for 2 hours. The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride followed by methylene chloride/ethyl acetate/methanol (45/50/5 followed by 40/50/10). The fractions containing the expected product were combined and evaporated to give 1-(4-fluoroindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine (57 mg, 22 %).

¹H NMR Spectrum: (DMSO-d₆) 4.66 (s, 2H); 6.57 (s, 1H); 7.15 (dd, 1H); 7.35 (m, 3H); 7.5 (m, 1H); 8.12 (m, 2H); 8.3 (m, 1H); 8.48 (d, 2H); 8.5 (m, 1H)

MS - ESI: 371.6 [MH]⁺

The starting material was prepared as follows:

A mixture of 2-fluoro-4-nitrophenol (15g, 95.5 mmol) and benzyl bromide (18g, 105 mmol) in acetone (125 ml) containing potassium carbonate (26.5 g, 190 mmol) was heated at reflux for 2 hours. The volatiles were removed and the residue was partitioned between 2N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water,

brine, dried (MgSO₄) and the volatiles were removed under vacuum. The solid was triturated with petroleum ether to give 2-fluoro-4-nitro-benzyloxybenzene (23g, 97%).

¹H NMR Spectrum: (CDCl₃) 5.3 (s, 2H); 7.1 (t, 1H); 7.35-7.55 (m, 5H); 8.0 (m, 2H)

To a solution of potassium *tert*-butoxide (1.72g, 15.4 mmol) in DMF (15 ml) cooled at -30°C, was added dropwise a solution of 2-fluoro-4-nitro-benzyloxybenzene (1.73g, 7 mmol) and 4-chlorophenoxyacetonitrile (1.29 g, 7.7 mmol) while maintaining the temperature below

-79-

-25°C. After completion of addition, the mixture was stirred for 30 minutes at -20°C and then poured onto a mixture of cold 1N hydrochloric acid and ether. The organic layer was separated, washed with 1N sodium hydroxide, followed by water, brine and dried ($MgSO_4$). The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/petroleum ether (3/1) to give a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene (1.2 g, 60%).

1 1H NMR Spectrum: (DMSO d_6) 4.22 (s, 2H, 3-cyanomethyl isomer); 4.3 (s, 2H, 5-cyanomethyl isomer); 5.32 (s, 2H, 5-cyanomethyl isomer); 5.36 (s, 2H, 3-cyanomethyl isomer); 7.3-7.7 (m, 6H); 8.1 (d, 1H, 3-cyanomethyl isomer); 8.2 (d, 1H, 5-cyanomethyl isomer)

A solution of a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene (23g, 80.4 mmol) in ethanol (220ml) and acetic acid (30ml) containing 10% palladium on charcoal (600mg) was hydrogenated under 3 atmospheres pressure until hydrogen uptake ceased. The mixture was filtered and the filtrate was evaporated under vacuum. The residue was purified on column chromatography using a Prochrom® equipment eluting with methylene chloride/petroleum ether (20/80) to give 4-fluoro-5-hydroxyindole (2.48g) and 6-fluoro-5-hydroxyindole (3.5 g).

4-fluoro-5-hydroxyindole:

20 1H NMR Spectrum: (DMSO d_6) 6.32 (s, 1H); 6.75 (dd, 1H); 7.0 (d, 1H); 7.28 (dd, 1H); 8.8 (br s, 1H); 11.05 (br s, 1H)

6-fluoro-5-hydroxyindole:

1H NMR Spectrum: (DMSO d_6) 6.25 (s, 1H); 7.0 (d, 1H); 7.12 (d, 1H); 7.2 (dd, 1H); 9.0 (br s, 1H)

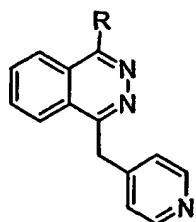
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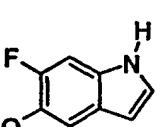
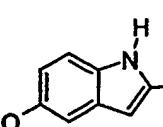
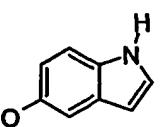
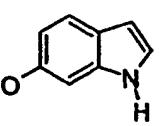
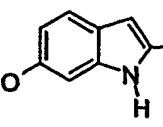
Examples 2-8

Using an analogous procedure to that described in Example 1, 1-chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with the appropriate hydroxyindole (0.7 mmol) to give the corresponding compounds described in Table I:

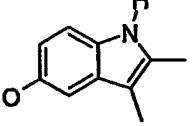
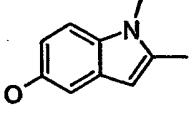
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-80-

**Table I**

Example	Weight (mg)	Yield (%)	MS-ESI [MH] ⁺	R	Note
2	75	29	371.6		a
3	106	41	367.6		b
4	73	29	353.6		c
5	86	35	353.6		d
6	110	43	367.6		e

-81-

Example	Weight (mg)	Yield (%)	MS-ESI [MH] ⁺	R	Note
7	88	33	381.6		f
8	89	33	381.6		g

a) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 6-fluoro-5-hydroxyindole (106 mg, 0.7 mmol), (prepared as described for the starting material in Example 1), to give 1-(6-fluoroindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine.

5 ¹H NMR Spectrum: (DMSO_d₆) 4.65 (s, 2H) ; 6.5 (s, 2H) ; 7.32 (d, 2H) ; 7.4 (d, 1H) ; 7.45 (s, 1H) ; 7.62 (d, 1H) ; 8.1 (m, 2H) ; 8.3 (m, 1H) ; 8.48 (d, 2H) ; 8.5 (m, 1H)

b) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 5-hydroxy-2-methylindole (104 mg, 0.7 mmol) to give 1-(2-methylindol-5-yloxy)-4-(4-

10 pyridylmethyl)phthalazine.

1H NMR Spectrum: (DMSO_d₆) 2.42 (s, 3H) ; 4.65 (s, 2H) ; 6.18 (s, 1H) ; 6.95 (dd, 1H) ; 7.32 (m, 4H) ; 8.1 (m, 2H) ; 8.25 (m, 1H) ; 8.48 (m, 3H)

c) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 5-hydroxyindole (94 mg, 0.7 mmol) to give 1-(indol-5-yloxy)-4-(4-pyridylmethyl)phthalazine.

1H NMR Spectrum: (DMSO_d₆) 4.65 (s, 2H) ; 6.48 (s, 1H) ; 7.05 (dd, 1H) ; 7.32 (d, 2H) ; 7.4-7.5 (m, 3H) ; 8.07 (m, 2H) ; 8.25 (m, 1H) ; 8.4-8.5 (m, 3H)

d) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 6-hydroxyindole (94

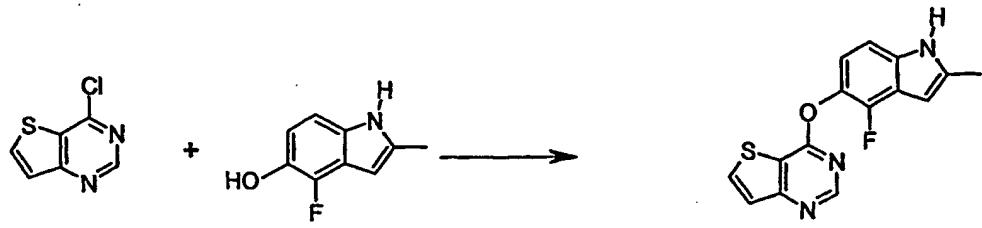
20 mg, 0.7 mmol) to give 1-(indol-6-yloxy)-4-(4-pyridylmethyl)phthalazine.

-82-

¹H NMR Spectrum: (DMSO_d₆) 4.65 (s, 2H) ; 6.5 (s, 1H) ; 6.98 (dd, 1H) ; 7.35 (d, 2H) ; 7.37 (s, 1H) ; 7.4 (m, 1H) ; 7.6 (d, 1H) ; 8.1 (m, 2H) ; 8.28 (m, 1H) ; 8.4-8.5 (m, 3H)

- e) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 6-hydroxy-2-methylindole (104 mg, 0.7 mmol), (Eur. J. Med. Chem. 1975, 10, 187), to give 1-(2-methylindol-6-yloxy)-4-(4-pyridylmethyl)phthalazine.
- ¹H NMR Spectrum: (DMSO_d₆) 2.41 (s, 3H) ; 4.65 (s, 2H) ; 6.18 (s, 1H) ; 6.9 (dd, 1H) ; 7.21 (s, 1H) ; 7.32 (d, 2H) ; 7.45 (d, 1H) ; 8.05-8.15 (m, 2H) ; 8.25 (m, 1H) ; 8.4-8.5 (m, 3H)
- f) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 2,3-dimethyl-5-hydroxyindole (113 mg, 0.7 mmol), (Arch. Pharm. 1972, 305, 159), to give 1-(2,3-dimethylindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine.
- ¹H NMR Spectrum: (DMSO_d₆) 2.15 (s, 3H) ; 2.35 (s, 3H) ; 4.65 (s, 2H) ; 6.93 (dd, 1H) ; 7.2-7.4 (m, 4H) ; 8.0-8.12 (m, 2H) ; 8.25 (m, 1H) ; 8.4-8.5 (m, 3H)
- g) 1-Chloro-4-(4-pyridylmethyl)phthalazine (150 mg) was reacted with 1,2-dimethyl-5-hydroxyindole (113 mg, 0.7 mmol), (Tetrahedron, 1994, 50, 13433), to give 1-(1,2-dimethylindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine.
- ¹H NMR Spectrum: (DMSO_d₆) 2.45 (s, 3H) ; 3.72 (s, 3H) ; 4.64 (s, 2H) ; 6.25 (s, 1H) ; 7.03 (dd, 1H) ; 7.32 (d, 2H) ; 7.35 (s, 1H) ; 7.46 (d, 1H) ; 8.02-8.1 (m, 2H) ; 8.25 (m, 1H) ; 8.46 (m, 3H)

Example 9



25

11

15

12

Using an analogous procedure to that described in Example 1,

-83-

4-chlorothieno[3,2-d]pyrimidine (150 mg, 0.88 mmol) was reacted with 4-fluoro-5-hydroxy-2-methylindole (174 mg, 1.05 mmol) to give

4-(4-fluoro-2-methylindol-5-yloxy)thieno[3,2-d]pyrimidine (18 mg, 7 %).

¹H NMR Spectrum: (DMSO_d₆) 2.41 (s, 3H) ; 6.25 (s, 1H) ; 7.03 (dd, 1H) ; 7.18 (d, 1H) ; 7.75 (d, 1H) ; 8.5 (d, 1H) ; 8.68 (s, 1H)

MS - ESI: 300 [MH]⁺

The starting material was prepared as follows :

To a suspension of sodium hydride (5.42 g, 226 mmol) (prewashed with pentane) in
10 THF (100 ml) cooled at 10°C was added ethyl acetoacetate (29.4 g, 226 mmol) while keeping the temperature below 15°C. After completion of addition, the mixture was further stirred for 15 minutes and cooled to 5°C. A solution of 1,2,3-trifluoro-4-nitrobenzene (20 g, 113 mmol) in THF (150 ml) was added while keeping the temperature below 5°C. The mixture was then left to warm up to ambient temperature and stirred for 24 hours. The volatiles were removed
15 under vacuum and the residue was partitioned between ethyl acetate and 2N aqueous hydrochloric acid. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was dissolved in concentrated hydrochloric acid (650 ml) and acetic acid (600 ml) and the mixture was heated at reflux for 15 hours. After cooling, the volatiles were removed under vacuum and the residue was partitioned between aqueous sodium
20 hydrogen carbonate (5 %) and ethyl acetate. The organic layer was washed with sodium hydrogen carbonate, water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (75/25) to give 3-acetyl methyl-1,2-difluoro-4-nitrobenzene (17.5 g, 72 %).

¹H NMR Spectrum: (CDCl₃) 2.4 (s, 3H) ; 4.25 (s, 2H) ; 7.25 (dd, 1H) ; 8.0 (dd, 1H)

25 A solution of 3-acetyl methyl-1,2-difluoro-4-nitrobenzene (500 mg, 2.3 mmol) in methylene chloride (5 ml) containing montmorillonite K10 (1 g) and trimethyl orthoformate (5 ml) was stirred for 24 hours at ambient temperature. The solid was filtered, washed with methylene chloride and the filtrate was evaporated to give 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 88 %).

30 ¹H NMR Spectrum: (CDCl₃) 1.2 (s, 3H) ; 3.2 (s, 6H) ; 3.52 (s, 2H) ; 7.18 (dd, 1H) ; 7.6 (m, 1H)

-84-

To a solution of benzyl alcohol (221 mg, 2.05 mmol) in DMA (1.5 ml) was added 60% sodium hydride (82 mg, 2.05 mmol). The mixture was stirred for 1 hour at ambient temperature. A solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 2.05 mmol) in DMA (1.5 ml) was added and the mixture was stirred for 3 hours at ambient 5 temperature. The mixture was diluted with 1N hydrochloric acid (10 ml) and extracted with ethyl acetate. The organic layer was evaporated and the residue was dissolved in THF (2 ml) and 6N hydrochloric acid (0.3 ml) was added. The mixture was stirred for 1 hour at ambient temperature and the solvents were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried 10 (MgSO_4) and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 3-acetymethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (350 mg, 56 %).

^1H NMR Spectrum: (CDCl_3) 2.35 (s, 3H) ; 4.25 (s, 2H) ; 5.25 (s, 2H) ; 7.0 (dd, 1H) ; 7.32-7.5 (m, 5H) ; 8.0 (dd, 1H)

15 A solution of 3-acetymethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (300 mg, 0.99 mmol) in ethanol (10 ml) and acetic acid (1 ml) containing 10 % palladium on charcoal (30 mg) was hydrogenated at 2 atmospheres pressure for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the organic layer was washed with aqueous sodium hydrogen carbonate, brine and evaporated to give 4-fluoro-20 5-hydroxy-2-methylindole. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (63 mg, 30%).
MS-ESI : 166 [MH]⁺

^1H NMR Spectrum: (DMSO_d_6) 2.35 (s, 3H) ; 6.05 (s, 1H) ; 6.65 (dd, 1H) ; 6.9 (d, 1H) ; 8.75 (s, 1H) ; 10.9 (s, 1H)

25 ^{13}C NMR Spectrum: (DMSO_d_6) 13.5 ; 94.0 ; 106.0 ; 112 ; 118.5 (d) ; 132 (d) ; 136 (d) ; 136.5 ; 142.5 (d)

Alternatively the 4-fluoro-5-hydroxy-2-methylindole may be prepared as follows:

To a solution of 2-fluoro-4-nitroanisole (9.9 g, 58 mmol) and 4-30 chlorophenoxyacetonitrile (10.7 g, 64 mmol) in DMF (50 ml) cooled at -15°C was added potassium *tert*-butoxide (14.3 g, 127 mmol) in DMF (124 ml). After stirring for 30 minutes at -15°C, the mixture was poured onto cooled 1N hydrochloric acid. The mixture was extracted

-85-

with ethyl acetate. The organic layer was washed with 1N sodium hydroxide, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride. The fractions containing the expected product were combined and evaporated. The residue was dissolved in ethanol (180 ml) and acetic acid (24 ml) containing 5 10 % palladium on charcoal (600 mg) and the mixture was hydrogenated under 3 atmospheres pressure for 2 hours. The mixture was filtered, and the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed with saturated sodium hydrogen carbonate followed by brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with 10 methylene chloride to give a mixture of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole (5.64 g, 59 %) in a ratio 1/2.

1H NMR Spectrum: (DMSO d_6) 3.85 (s, 3H) ; 6.38 (s, 1H, 6-Fluoro) ; 6.45 (s, 1H ; 4-Fluoro) ; 6.9-7.4 (m, 3H)

A solution of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole in a ratio 1/2 15 (496 mg, 3 mmol), di-*tert*butyl dicarbonate (720 mg, 3.3 mmol) in acetonitrile (12 ml) containing DMAP (18 mg, 0.15 mmol) was stirred at ambient temperature for 24 hours. The volatiles were removed under vacuum. The residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid, followed by water, brine, dried ($MgSO_4$) and evaporated to give a mixture of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (702 mg, 88 %).

1H NMR Spectrum: (DMSO d_6) 1.65 (s, 9H) ; 3.9 (s, 3H) ; 6.6 (d, 1H, 6-fluoro) ; 6.72 (d, 1H, 4-fluoro) ; 7.2 (t, 1H, 6-fluoro) ; 7.4 (d, 1H, 4-fluoro) ; 7.62 (d, 1H, 6-fluoro) ; 7.68 (d, 1H, 4-fluoro) ; 7.78 (s, 1H, 4-fluoro) ; 7.85 (s, 1H, 6-fluoro)

To a solution of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (8.1 g, 30.5 mmol) in THF (100 ml) 25 cooled at -65°C was added *tert*-butyllithium (1.7 M) (23 ml, 35.7 mmol). After stirring for 4 hours at -70°C, methyl iodide (8.66 g, 61 mmol) was added and the mixture was left to warm-up to ambient temperature. Water was added and the mixture was extracted with ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated and was used 30 directly in the next step.

The crude product was dissolved in methylene chloride (100 ml) and TFA (25 ml) was added. After stirring for 1 hour at ambient temperature, the volatiles were removed under

vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with 1N sodium hydroxide, followed by water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (3/7) to give 6-fluoro-5-methoxy-2-methylindole (1.6 g) and 4-fluoro-5-methoxy-2-methylindole (0.8 5 g, 48 %).

6-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.05 (s, 1H) ; 7.1 (s, 1H) ; 7.12 (s, 1H) ; 10.8 (s, 1H)

10 4-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.15 (s, 1H) ; 6.9 (t, 1H) ; 7.05 (d, 1H) ; 11.0 (s, 1H)

To a solution of 4-fluoro-5-methoxy-2-methylindole (709 mg, 3.95 mmol) in 15 methylene chloride (9 ml) cooled at -30°C was added a solution of boron tribromide (2.18 g, 8.7 mmol) in methylene chloride (1 ml). After stirring for 1 hour at ambient temperature, the mixture was poured onto water and was diluted with methylene chloride. The pH of the aqueous layer was adjusted to 6. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting 20 with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (461 mg, 70 %).

MS-ESI : 166 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆) 2.35 (s, 3H) ; 6.05 (s, 1H) ; 6.65 (dd, 1H) ; 6.9 (d, 1H) ; 8.75 (s, 1H) ; 10.9 (s, 1H)

25 ¹³C NMR Spectrum: (DMSO_d₆) 13.5 ; 94.0 ; 106.0 ; 112 ; 118.5 (d) ; 132 (d) ; 136 (d) ; 136.5 ; 142.5 (d)

Alternatively the 4-fluoro-5-hydroxy-2-methylindole may be prepared as follows:

A solution of sodium methoxide (freshly prepared from sodium (1.71g) and methanol 30 (35ml)) was added to a solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (16.2 g, 62 mmol), (prepared as described above), in methanol (200ml) cooled at 5°C. The mixture was left to warm to ambient temperature and was stirred for 3 days. The volatiles were

-87-

removed under vacuum and the residue was partitioned between ethyl acetate and 2N hydrochloric acid (1ml). The organic layer was concentrated to a total volume of 100ml and THF (100ml) and 6N hydrochloric acid (25ml) were added. The mixture was stirred for 1 hour at ambient temperature. The volatiles were removed under vacuum and the residue was 5 partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (12.7 g, 90%).

MS-ESI : 250 [MNa]⁺

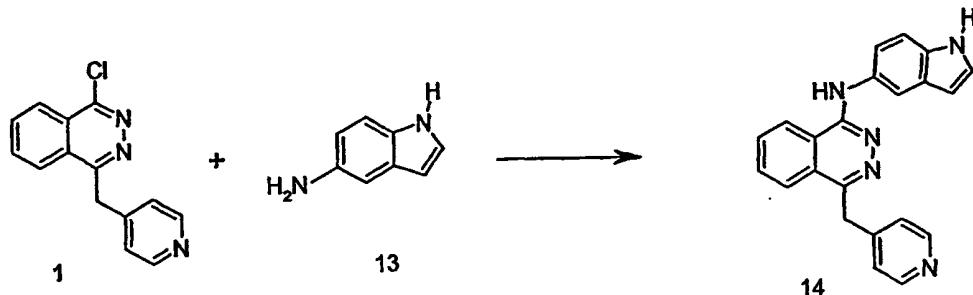
- 10 1H NMR Spectrum: ($CDCl_3$) 2.38 (s, 3H); 4.0 (s, 3H); 4.25 (s, 2H); 7.0 (dd, 1H); 8.05 (d, 1H)

To a solution of 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (11.36g, 50 mmol) in acetone (200ml) was added 4M aqueous ammonium acetate (700ml) followed by a solution of titanium trichloride (15% in water, 340ml) dropwise. The mixture was stirred for 15 10 minutes at ambient temperature and the mixture was extracted with ether. The organic layer was washed with 0.5N aqueous sodium hydroxide followed by water, brine, dried ($MgSO_4$) and the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride to give 4-fluoro-5-methoxy-2-methylindole (8.15g, 90%).

- 20 1H NMR Spectrum: (DMSO) 2.35 (s, 3H); 3.8 (s, 3H); 6.1 (s, 1H); 6.85 (dd, 1H); 7.02 (d, 1H)

Cleavage of 4-fluoro-5-methoxy-2-methylindole with boron tribromide to give 4-fluoro-5-hydroxy-2-methylindole is described above.

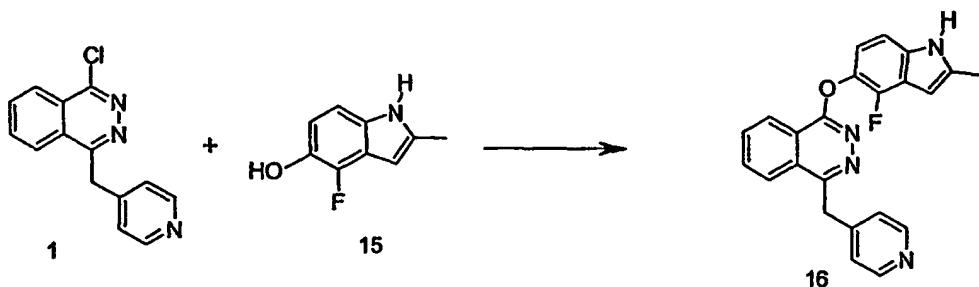
25 Example 10



To a solution of 1-chloro-4-(4-pyridylmethyl)phthalazine (85 mg, 0.33 mmol), (J. Med. Chem. 2000, 43, 2310-2323), and 5-aminoindole (53 mg, 0.39 mmol) in isopropanol (5 ml) was added 5.5N HCl in isopropanol (70 µl). After stirring for 4 hours at 85°C, the solid 5 was filtered, washed with isopropanol followed by ether and dried under vacuum to give 1-(indol-5-ylamino)-4-(4-pyridylmethyl)phthalazine hydrochloride (52 mg, 37 %).

¹H NMR Spectrum: (DMSO d₆) 4.6 (s, 2H) ; 6.55 (s, 1H) ; 7.25 (dd, 1H) ; 7.42 (d, 2H) ; 7.48 (t, 1H) ; 7.58 (d, 1H) ; 7.78 (s, 1H) ; 8.18 (m, 2H) ; 8.3 (m, 1H) ; 8.52 (d, 2H) ; 9.0 (m, 1)
MS - ESI: 352 [MH]⁺

10

Example 11

Under nitrogen a solution of 1-chloro-4-(4-pyridylmethyl)phthalazine (160 mg, 0.62
15 mmol), (J. Med. Chem. 2000, 43, 2310-2323), 4-fluoro-5-hydroxy-2-methylindole (124 mg,
0.75 mmol), (prepared as described for the starting material in Example 9), and cesium
carbonate (408 mg, 1.2 mmol) in DMF (4 ml) was heated at 95°C for 1.5 hours. After
cooling, the mixture was filtered and the volatiles were removed under vacuum. The residue
was purified by column chromatography, eluting with methylene chloride, followed by
20 methylene chloride/ethyl acetate/methanol (45/50/5). The fractions containing the expected
product were combined and evaporated. The residue was triturated with ether, and the solid
was filtered, washed with ether and dried under vacuum to give 1-(4-fluoro-2-methylindol-5-
yloxy)-4-(4-pyridylmethyl)phthalazine (98 mg, 41 %).

¹H NMR Spectrum: (CDCl₃) 2.42 (s, 3H) ; 4.61 (s, 2H) ; 6.28 (s, 1H) ; 7.02 (s, 1H) ; 7.04 (d,
25 1H) ; 7.24 (d, 2H) ; 7.8-8.0 (m, 3H) ; 8.3 (br s, 1H) ; 8.49 (d, 2H) ; 8.54 (d, 1H)
MS - ESI: 385 [MH]⁺

Example 12

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

5

	<u>(a) Tablet I</u>	<u>mg/tablet</u>
	Compound X	100
	Lactose Ph.Eur.....	182.75
	Croscarmellose sodium	12.0
10	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate.....	3.0

10

	<u>(b) Tablet II</u>	<u>mg/tablet</u>
	Compound X	50
15	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate.....	3.0

20

	<u>(c) Tablet III</u>	<u>mg/tablet</u>
	Compound X	1.0
	Lactose Ph.Eur.....	93.25
	Croscarmellose sodium	4.0
25	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate.....	1.0

25

	<u>(d) Capsule</u>	<u>mg/capsule</u>
	Compound X	10
	Lactose Ph.Eur.....	488.5
30	Magnesium stearate.....	1.5

30

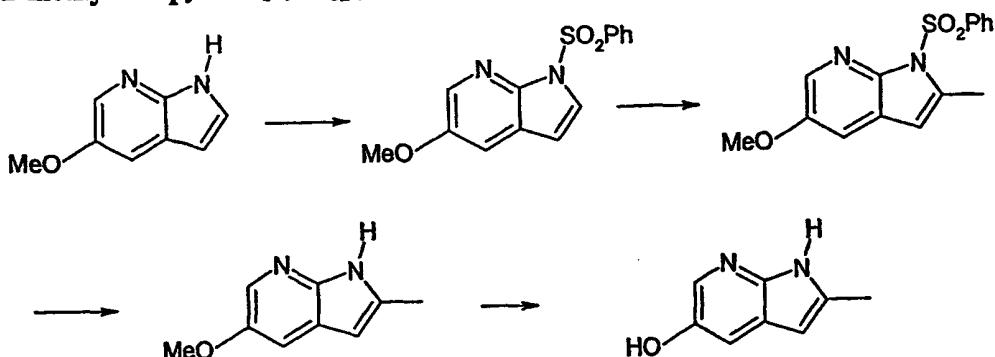
-90-

- (e) Injection I (50 mg/ml)
- Compound X 5.0% w/v
1N Sodium hydroxide solution 15.0% v/v
0.1N Hydrochloric acid
5 (to adjust pH to 7.6)
Polyethylene glycol 400 4.5% w/v
Water for injection to 100%
- (f) Injection II 10 mg/ml)
- 10 Compound X 1.0% w/v
Sodium phosphate BP 3.6% w/v
0.1N Sodium hydroxide solution 15.0% v/v
Water for injection to 100%
- 15 (g) Injection III (1mg/ml buffered to pH6)
- Compound X 0.1% w/v
Sodium phosphate BP 2.26% w/v
Citric acid 0.38% w/v
Polyethylene glycol 400 3.5% w/v
20 Water for injection to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for
25 example to provide a coating of cellulose acetate phthalate.

-91-

Reference Example 12-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-ol

- 5 To a solution of 5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (920 mg, 6.2 mmol) (Heterocycles 50, (2) 1065-1080, 1999) in methylene chloride (20ml) was added benzyltriethylammonium chloride (37 mg, 0.16 mmol) followed by sodium hydroxide powder (771 mg, 19.2 mmol). The mixture was cooled to 0°C and benzylsulfonyl chloride (991 µl, 7.77 mmol) was added dropwise. The mixture was stirred at 0°C for 15 minutes followed by 10 2 hours at ambient temperature. The mixture was filtered over diatomaceous earth and the filtrate was evaporated under vacuum. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (20/80 followed by 30/70). The fractions containing the expected product were combined and evaporated to give 5-methoxy-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1.69 g ; 94%)
- 15 ¹H NMR Spectrum: (DMSO d₆) 3.86 (s, 3H) ; 6.78 (d, 1H) ; 7.6-7.7 (m, 3H) ; 7.72 (dd, 1H) ; 7.88 (d, 1H) ; 8.02-8.12 (m, 3H)
- MS: 289.47 [M+H]⁺
- A solution of 5-methoxy-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (900 mg, 3.12 mmol) in THF (22.5 ml) was added dropwise to a solution of lithium diisopropylamide 20 (prepared from nBu-Li (2.5M in hexane) ; 2.5 ml) and diisopropylamine (874 µl) in THF (13.5 ml) cooled at -25°C and the mixture was stirred for 30 minutes. Methyl iodide (215 µl, 3.44 mmol) in THF (9 ml) was then added dropwise and the mixture was stirred for 10 minutes at -25°C, left to warm up to ambient temperature and stirred for 15 minutes. The mixture was then poured onto ice/water. The mixture was then extracted with ethyl acetate.
- 25 The organic layer was separated, washed with water, brine, dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl

-92-

acetate/petroleum ether (20/80 followed by 30/70). The fractions containing the expected product were combined and evaporated to give 5-methoxy-2-methyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (805 mg, 85%).

¹H NMR Spectrum: (DMSO_d₆) 2.7 (s, 3H) ; 3.82 (s, 3H) ; 6.51 (d, 1H) ; 7.49 (d, 1H) ; 7.59
5 (dd, 2H) ; 7.7 (m, 1H) ; 8.0-8.1 (m, 3H)

MS: 303.5 [M+H]⁺

A solution of 5-methoxy-2-methyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (950 mg, 3.14 mmol) and 40% aqueous sodium hydroxyde (106 ml) in methanol (160 ml) was heated at reflux for 30 minutes. After cooling, the mixture was poured onto cooled water and 10 extracted with ethyl acetate. The organic layer was separated, washed with water, brine, dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (1/1). The fractions containing the expected product were combined and evaporated to give 5-methoxy-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (462 mg, 91%).

15 ¹H NMR Spectrum: (DMSO d₆) 2.38 (s, 3H) ; 3.8 (s, 3H) ; 6.06 (d, 1H) ; 7.39 (d, 1H) ; 7.82 (d, 1H)

MS: 163.3 [M+H]⁺

A solution of boron tribromide (64 μ l, 0.68 mmol) in methylene chloride (200 μ l) was added to a solution of 5-methoxy-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg, 0.308 mmol) in 20 methylene chloride (4 ml) cooled at -30°C. The mixture was left to warm up to ambient temperature and further stirred for 3 hours. The mixture was poured onto ice. The pH was adjusted to 6.2 with 6N aqueous sodium hydroxide followed by 2 N aqueous hydrogen chloride. The mixture was extracted with ethyl acetate. The organic layer was washed with water, followed by brine and dried (MgSO₄), filtered and the filtrate was evaporated. The 25 residue was purified by column chromatography, eluting with with methylene chloride followed by methylene chloride/methanol (98/2 followed by 95/5). The fractions containing the expected product were combined and evaporated to give 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-ol (45 mg, quantitative).

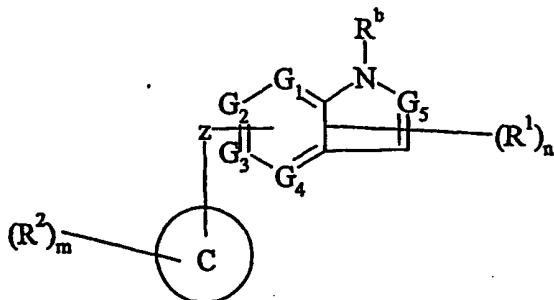
¹H NMR Spectrum: (DMSO d₆) 2.4 (s, 3H) ; 5.96 (s, 1H) ; 7.12 (d, 1H) ; 7.69 (d, 1H) ; 8.9 (s, 30 1H) ; 11.07 (br s, 1H)

MS: 149.2 [M+H]⁺

CLAIMS

1. The use of a compound of the formula I:

5



10

(I)

wherein:

- 15 ring C is a 9 or 10-membered bicyclic heteroaromatic group containing at least one nitrogen atom in the ring attached to Z and optionally containing a further 1-3 heteroatoms, selected independently from O, S and N, with the proviso that ring C is not a quinazoline, quinoline or cinnoline group;
either any one of G₁, G₂, G₃, G₄ and G₅ is nitrogen and the other four are -CH-,
- 20 or G₁, G₂, G₃, G₄ and G₅ are all -CH-;
Z is -O-, -NH- or -S-; Z is linked to any one of G₁, G₂, G₃ and G₄ which is a free carbon atom;
- n is an integer from 0 to 5; any of the substituents R¹ may be attached at any free carbon atom of the indole, azaindole or indazole group, such free carbon atoms may be G₁, G₂, G₃, G₄ or G₅ or may be at the 3-position of the indole, azaindole or indazole group;
- 25 m is an integer from 0 to 2;
- R^b represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₃alkylaminoC₁₋₄alkyl, di(C₁₋₃alkyl)aminoC₁₋₄alkyl, C₂₋₅alkenylaminoC₁₋₄alkyl, C₂₋₅alkynylaminoC₁₋₄alkyl, -C₁₋₅alkyl(ring A) wherein ring A is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino and wherein ring A may bear one or more substituents selected from C₁₋₄alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, hydroxy, oxo, halogeno, cyano, cyanoC₁₋₄alkyl, C₁₋₄alkylsulphonyl and C₁₋₄alkanoyl;

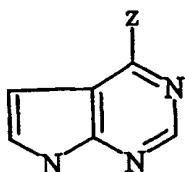
- R^1 represents hydrogen, oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, amino C_{1-4} alkyl, C_{1-3} alkylamino C_{1-4} alkyl, di(C_{1-3} alkyl)amino C_{1-4} alkyl, - C_{1-5} alkyl(ring B) wherein ring B is selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-
- 5 methylpiperazinyl, N-ethylpiperazinyl, morpholino and thiomorpholino;
- R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylsulphonyl, - NR^3R^4 (wherein R^3 and R^4 , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or R^5X^1 - (wherein X^1 represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁶C(O)-, -C(O)NR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -
- 10 NR^{10} - (wherein R^6 , R^7 , R^8 , R^9 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and R^5 is selected from one of the following twenty-two groups:
- 1) hydrogen, oxiranyl C_{1-4} alkyl or C_{1-5} alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
 - 2) C_{1-5} alkyl $X^2C(O)R^{11}$ (wherein X^2 represents -O- or -NR¹²- (in which R^{12} represents
- 15 hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{11} represents C_{1-3} alkyl, - $NR^{13}R^{14}$ or - OR^{15} (wherein R^{13} , R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-5} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 3) C_{1-5} alkyl X^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, -SO₂-, -OC(O)-, -NR¹⁷C(O)-, -C(O)NR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R^{17} , R^{18} , R^{19} , R^{20} and R^{21} each
- 20 independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{16} represents hydrogen, C_{1-3} alkyl, cyclopentyl, cyclohexyl or a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3} alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}
- 25 cyanoalkyl, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl, C_{1-4} alkoxycarbonyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkylamino C_{1-4} alkoxy, di(C_{1-4} alkyl)amino C_{1-4} alkoxy and a group -(O)_f(C_{1-4} alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2
- 30 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4} alkyl));
- 4) C_{1-5} alkyl X^4C_{1-5} alkyl X^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³C(O)-, -C(O)NR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein

- R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R^{22} represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R^{28} (wherein R^{28} is a 4-, 5- or 6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $-(O)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 10) C_{1-5} alkylR²⁸ (wherein R²⁸ is as defined herein);
- 15) 7) C_{2-5} alkenylR²⁸ (wherein R²⁸ is as defined herein);
- 8) C_{2-5} alkynylR²⁸ (wherein R²⁸ is as defined herein);
- 9) R^{29} (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁰R³¹, -NR³²C(O)R³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group $-(O)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 20) 10) C_{1-5} alkylR²⁹ (wherein R²⁹ is as defined herein);
- 25) 11) C_{2-5} alkenylR²⁹ (wherein R²⁹ is as defined herein);
- 12) C_{2-5} alkynylR²⁹ (wherein R²⁹ is as defined herein);
- 30) 13) C_{1-5} alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);

- 14) $C_{2-5}\text{alkenyl}X^7R^{29}$ (wherein X^7 represents -O-, -S-, -SO-, -SO₂-, -NR³⁹C(O)-, -C(O)NR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 5 15) $C_{2-5}\text{salkynyl}X^8R^{29}$ (wherein X^8 represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴C(O)-, -C(O)NR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 16) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{29}$ (wherein X^9 represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹C(O)-, -C(O)NR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 10 17) $C_{1-4}\text{alkyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined herein);
- 18) $C_{2-5}\text{alkenyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 15 19) $C_{2-5}\text{salkynyl}$ which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20 20) $C_{2-5}\text{alkenyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined herein);
- 20 21) $C_{2-5}\text{salkynyl}X^9C_{1-4}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined herein); and
- 22) $C_{1-4}\text{alkyl}R^{54}(C_{1-4}\text{alkyl})_q(X^9)_rR^{55}$ (wherein X⁹ is as defined herein, q is 0 or 1, r is 0 or 1, and R⁵⁴ and R⁵⁵ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents
- 25 selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy
- 30 and a group $\text{--}(-\text{O})_f(C_{1-4}\text{alkyl})_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl), with the proviso that R⁵⁴ cannot be hydrogen);

and additionally wherein any C₁-alkyl, C₂-alkenyl or C₂-alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino); with the proviso that when ring C is

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wherein Z is as defined herein, (but Z is not a part of ring C, it is shown for the purposes of clarity), at least one R² does not have a value selected from hydrogen, halogeno, C₁-alkyl, C₁-alkoxy and NR^cR^d (wherein each of R^c and R^d independently represents hydrogen, C₁-alkyl or phenyl which phenyl may bear 1-3 substituents selected from halogeno, trifluoromethyl,

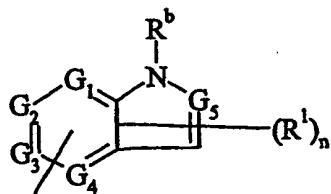
15 C₁-alkyl and C₁-alkoxy);

or a salt thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

20

2. The use of a compound according to claim 1 wherein the optionally substituted indole moiety of formula II:

25



(II)

wherein R¹, R^b, G₁, G₂, G₃, G₄, G₅ and n are as defined in claim 1;

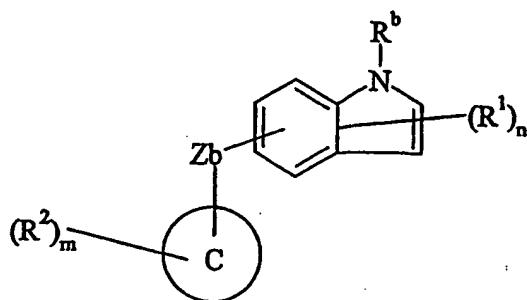
is selected from the indole moieties:

30 4-fluoro-2-methylindol-5-yl, 2-methylindol-5-yl, 2-methylindol-6-yl, 2,3-dimethylindol-5-yl, 1-methylindol-5-yl, 1,2-dimethylindol-5-yl, 4-fluoroindol-5-yl, 6-fluoroindol-5-yl, indol-5-yl and 3-methylindol-5-yl.

-98-

3. A compound of the formula Ib:

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(Ib)

wherein ring C, R^b, R¹, R², m and n are as defined in claim 1 and Zb represents -O-, -NH- or -S-;

15 with the proviso that if Zb is -NH- then:

at least one R² is not selected from hydrogen, chloro, bromo, methyl, phenyl(hydroxymethyl), dimethylamino, methylsulphanyl, methylsulphinyl, methylsulphonyl and hydroxycyclohexylamino;

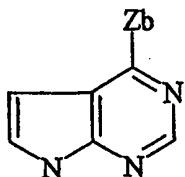
20 X¹ is not selected from -CH₂- a direct bond and -C(O)NR⁷-, wherein R⁷ and X¹ are as defined in claim 1; and

where R² is a group R⁵-X¹ and X¹ is -NR⁶C(O)- or -NR⁹SO₂-, R⁵ does not contain an alkenyl or alkynyl moiety, wherein R⁵, R⁶, R⁹ and X¹ are as defined in claim 1;

and with the further proviso that when ring C is

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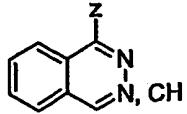
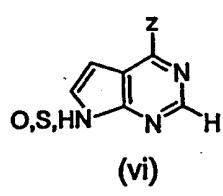
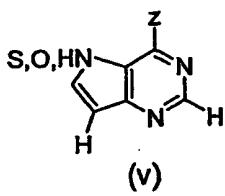
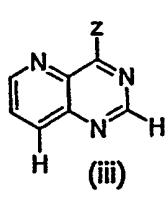
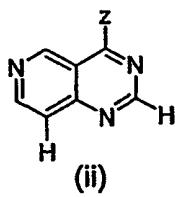
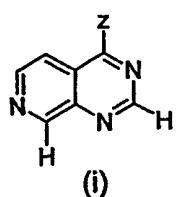
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wherein Zb is as defined herein, (but Zb is not a part of ring C, it is shown for the purposes of clarity), at least one R² does not have a value selected from hydrogen, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and NR^cR^d (wherein each of R^c and R^d independently represents hydrogen, C₁₋₄alkyl or phenyl which phenyl may bear 1-3 substituents selected from halogeno, trifluoromethyl,

10 C₁₋₄alkyl and C₁₋₄alkoxy);

or a salt thereof.

4. A compound according to claim 3 wherein ring C is selected from one of the following seven moieties:



15

(vii)

wherein Z is Zb as defined in claim 3 but is not part of ring C.

5. A compound according to claim 3 or claim 4 wherein ring C is a

20 thienopyrimidine ring or a phthalazine ring.

6. A compound according to any one of claims 3 to 5
wherein Zb is -O- or -NH-.

5 7. A compound according to any one of claims 3 to 6
wherein R^b is hydrogen.

8. A compound according to any one of claims 3 to 7 wherein R¹ represents
methyl, ethyl, trifluoromethyl or halogeno.

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9. A compound according to any one of claims 3 to 8 wherein R² represents
hydroxy, halogeno, nitro, trifluoromethyl, C₁₋₃alkyl, cyano, amino or R⁵X¹- [wherein X¹ is as
defined in claim 1 and R⁵ is selected from one of the following twenty groups:
1) C₁₋₃alkyl which may be unsubstituted or which may be substituted with one or more groups
15 selected from fluoro, chloro and bromo, or C₂₋₃alkyl which may be unsubstituted or
substituted with one or more groups selected from hydroxy and amino;
2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-
methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-
(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-
20 methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl, or 2-(N-
methyl-N-(butoxycarbonyl)amino)ethyl;
3) C₂₋₃alkylX³R¹⁶ (wherein X³ is as defined in claim 1 and R¹⁶ is a group selected from C₁₋₃alkyl,
cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl,
imidazolidinyl and tetrahydropyrananyl which group is linked to X³ through a carbon atom and
25 which C₁₋₃alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C₁₋₂alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl,
imidazolidinyl or tetrahydropyrananyl group may bear one substituent selected from oxo,
hydroxy, halogeno, cyano, C₁₋₂cyanooalkyl, C₁₋₂alkyl, C₁₋₂hydroxyalkyl, C₁₋₂alkoxy, C₁₋₂alkoxyC₁₋₃alkyl,
C₁₋₂alkylsulphonylC₁₋₃alkyl, C₁₋₂alkoxycarbonyl, C₁₋₃alkylamino, di(C₁₋₃alkylaminoC₁₋₃alkyl),
30 C₁₋₃alkylamino, C₁₋₃alkylaminoC₁₋₃alkyl, di(C₁₋₃alkyl)aminoC₁₋₃alkyl, C₁₋₃alkylaminoC₁₋₃alkoxy, di(C₁₋₃alkyl)aminoC₁₋₃alkoxy and a group -(O)_f(C₁₋₃alkyl)_gringD (wherein f is 0 or
1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl,
piperidinyl, azetidinyl, morpholino and thiomorpholino));

-101-

- 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as defined in claim 1 and R^{22} represents hydrogen or $C_{1-2}alkyl$);
5) R^{28} (wherein R^{28} is as defined in claim 1);
5
6) $C_{1-3}alkylR^{59}$ (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, imidazolidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-3}alkyl$ through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkanoyl$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, $di(C_{1-3}alkyl)amino$, $C_{1-3}alkylaminoC_{1-3}alkyl$, $di(C_{1-3}alkyl)aminoC_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, $di(C_{1-3}alkyl)aminoC_{1-3}alkoxy$ and a group $\text{--}(-\text{O})_f(C_{1-3}alkyl)_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino)) or $C_{2-3}alkylR^{60}$ (wherein R^{60} is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-2}cyanoalkyl$, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$, $C_{1-2}alkoxy$, $C_{1-2}alkanoyl$, $C_{1-2}alkoxyC_{1-3}alkyl$, $C_{1-2}alkylsulphonyl$, $C_{1-2}alkylsulphonylC_{1-3}alkyl$, $C_{1-2}alkoxycarbonyl$, $C_{1-3}alkylamino$, $di(C_{1-3}alkyl)amino$, $C_{1-3}alkylaminoC_{1-3}alkyl$, $di(C_{1-3}alkyl)aminoC_{1-3}alkyl$, $C_{1-3}alkylaminoC_{1-3}alkoxy$, $di(C_{1-3}alkyl)aminoC_{1-3}alkoxy$ and a group $\text{--}(-\text{O})_f(C_{1-3}alkyl)_g\text{ringD}$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));
7) R^{29} (wherein R^{29} is as defined in claim 1);
25 8) $C_{1-4}alkylR^{29}$ (wherein R^{29} is as defined in claim 1);
9) $1-R^{29}\text{but-2-en-4-yl}$ (wherein R^{29} is as defined in claim 1);
10) $1-R^{29}\text{but-2-yn-4-yl}$ (wherein R^{29} is as defined in claim 1);
11) $C_{1-3}alkylX^6R^{29}$ (wherein X^6 and R^{29} are as defined in claim 1);
12) $1-(R^{29}X^7)\text{but-2-en-4-yl}$ (wherein X^7 and R^{29} are as defined in claim 1);
30 13) $1-(R^{29}X^8)\text{but-2-yn-4-yl}$ (wherein X^8 and R^{29} are as defined in claim 1);
14) $C_{2-3}alkylX^9C_{1-3}alkylR^{29}$ (wherein X^9 and R^{29} are as defined in claim 1);
15) $C_{2-3}alkylX^9C_{1-3}alkylR^{28}$ (wherein X^9 and R^{28} are as defined in claim 1);

- 16) C_{2-5} alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-4} alkylamino, N,N-di(C_{1-4} alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-5 di(C₁₋₄alkyl)aminosulphonyl;
- 17) C_{2-5} alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-4} alkylamino, N,N-di(C_{1-4} alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-5 di(C₁₋₄alkyl)aminosulphonyl;
- 18) C_{2-3} alkenyl X^9C_{1-3} alkyl R^{28} (wherein X^9 and R^{28} are as defined in claim 1);
- 19) C_{2-3} alkynyl X^9C_{1-3} alkyl R^{28} (wherein X^9 and R^{28} are as defined in claim 1); and
- 20) C_{1-3} alkyl $R^{54}(C_{1-3}$ alkyl) $_q(X^9)_rR^{55}$ (wherein X^9 , q , r , R^{54} and R^{55} are as defined in claim 1);
- 15 and additionally wherein any C_{1-5} alkyl, C_{2-5} alkenyl or C_{2-5} alkynyl group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino].

10. A compound selected from:

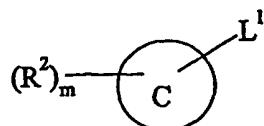
- 1-(4-fluoroindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine,
20 1-(indol-6-yloxy)-4-(4-pyridylmethyl)phthalazine,
1-(2-methylindol-6-yloxy)-4-(4-pyridylmethyl)phthalazine,
4-(4-fluoro-2-methylindol-5-yloxy)thieno[3,2-d]pyrimidine and
1-(4-fluoro-2-methylindol-5-yloxy)-4-(4-pyridylmethyl)phthalazine,
or a salt thereof.

25

11. A compound according to any one of claims 3 to 10 in the form of a pharmaceutically acceptable salt.

12. A process for the preparation of a compound of formula Ib or a salt thereof
30 which comprises:
(a) the reaction of a compound of the formula III:

-103-

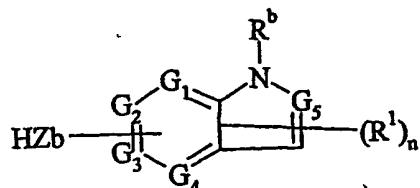


5

(III)

(wherein ring C, R^2 and m are as defined in claim 1 and L^1 is a displaceable moiety), with a
10 compound of the formula IV:

15



(IV)

(wherein R^b , R^1 and n are as defined in claim 1, G_1 , G_2 , G_3 , G_4 and G_5 are all -CH- and Zb is
20 as defined in claim 3);

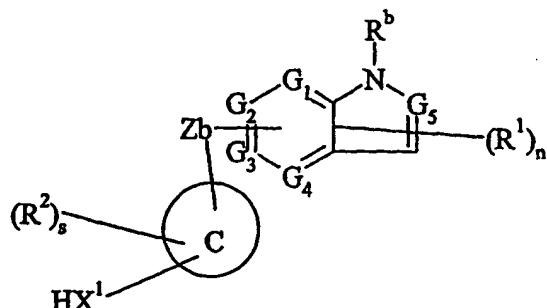
(b) a compound of formula Ib or a salt thereof wherein at least one R^2 is R^5X^1 wherein
 R^5 is as defined in claim 1 and X^1 is -O-, -S-, -OC(O)- or -NR¹⁰- (wherein R¹⁰ independently
represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) may be prepared by the reaction of a
compound of the formula V:

25

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-104-

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(V)

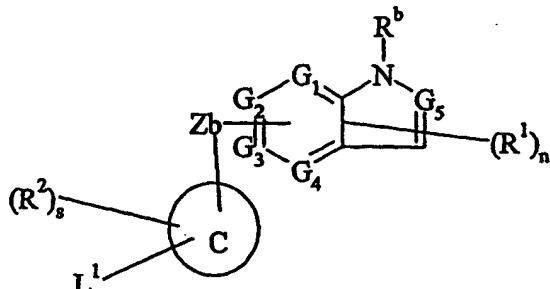
10 (wherein ring C , R^b , R^1 , R^2 and n are as defined in claim 1, G_1 , G_2 , G_3 , G_4 and G_5 are all -CH-, Zb is as defined in claim 3, X^1 is as herein defined in this section and s is 0 or 1) with a compound of formula VI:



15

(wherein R^5 is as defined in claim 1 and L^1 is as defined herein);
 (c) a compound of formula Ib or a salt thereof wherein at least one R^2 is R^5X^1 wherein
 20 R^5 is as defined in claim 1 and X^1 is -O-, -S-, -OC(O)- or -NR¹⁰- (wherein R¹⁰ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) may be prepared by the reaction of a compound of the formula VII:

25



(VII)

30

with a compound of the formula VIII:



(wherein ring C, R^b, R¹, R², R⁵ and n are all as defined in claim 1, G₁, G₂, G₃, G₄ and G₅ are all -CH-, Zb is as defined in claim 3, L¹ and s are as defined herein and X¹ is as herein defined in this section);

- 5 (d) a compound of formula Ib or a salt thereof wherein at least one R² is R⁵X¹ wherein X¹ is as defined in claim 1 and R⁵ is C₁₋₅alkylR⁶², wherein R⁶² is selected from one of the following nine groups:

1) X¹⁰C₁₋₃alkyl (wherein X¹⁰ represents -O-, -S-, -SO₂-, -NR⁶³C(O)- or -NR⁶⁴SO₂- (wherein R⁶³ and R⁶⁴ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

10 2) NR⁶⁵R⁶⁶ (wherein R⁶⁵ and R⁶⁶ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

3) X¹¹C₁₋₅alkylX⁵R²² (wherein X¹¹ represents -O-, -S-, -SO₂-, -NR⁶⁷C(O)-, -NR⁶⁸SO₂- or -NR⁶⁹- (wherein R⁶⁷, R⁶⁸, and R⁶⁹ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and X⁵ and R²² are as defined in claim 1);

15 4) R²⁸ (wherein R²⁸ is as defined in claim 1);

5) X¹²R²⁹ (wherein X¹² represents -O-, -S-, -SO₂-, -NR⁷⁰C(O)-, -NR⁷¹SO₂-, or -NR⁷²-

20 (wherein R⁷⁰, R⁷¹, and R⁷² which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined in claim 1); and

6) X¹³C₁₋₃alkylR²⁹ (wherein X¹³ represents -O-, -S-, -SO₂-, -NR⁷³C(O)-, -NR⁷⁴SO₂- or -NR⁷⁵- (wherein R⁷³, R⁷⁴ and R⁷⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined in claim 1);

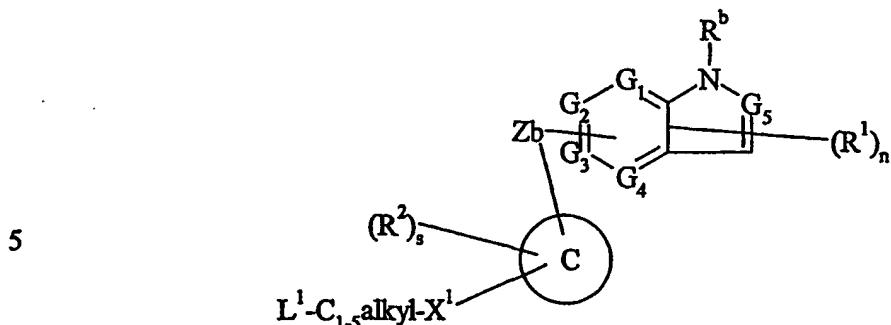
25 7) R²⁹ (wherein R²⁹ is as defined in claim 1);

8) X¹³C₁₋₄alkylR²⁸ (wherein X¹³ and R²⁸ are as defined in claim 1); and

9) R⁵⁴(C₁₋₄alkyl)_q(X⁹)_rR⁵⁵ (wherein q, r, X⁹, R⁵⁴ and R⁵⁵ are as defined in claim 1);

may be prepared by reacting a compound of the formula IX:

-106-



(IX)

10

(wherein ring C, X¹, R^b, R¹, R² and n are as defined in claim 1, G₁, G₂, G₃, G₄ and G₅ are all —CH—, Zb is as defined in claim 3 and L¹, and s are as defined herein) with a compound of the formula X:



15

(wherein R⁶² is as defined herein);

(e) a compound of the formula Ib or a salt thereof wherein one or more of the substituents (R²)_m is represented by —NR⁷⁶R⁷⁷, where one (and the other is hydrogen) or both of R⁷⁶ and R⁷⁷ are C₁₋₃alkyl, may be effected by the reaction of compounds of formula I wherein the
20 substituent (R²)_m is an amino group and an alkylating agent;

(f) a compound of the formula Ib or a salt thereof wherein X¹ is —SO— or —SO₂— may be prepared by oxidation from the corresponding compound in which X¹ is —S— or —SO— (when X¹
25 is —SO₂— is required in the final product);

and when a salt of a compound of formula Ib is required, reaction of the compound obtained with an acid or base whereby to obtain the desired salt.

13. A pharmaceutical composition which comprises a compound of the formula Ib
30 as defined in claim 3 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

-107-

14. A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I as defined in
5 claim 1 or a pharmaceutically acceptable salt thereof.